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HEAD INJURIES IN CHILDREN

OBSERVATIONS ON THEIR INCIDENCE AND CAUSES WITH AN ENQUIRY INTO THE VALUE OF ROUTINE SKULL X-RAYS

BY

JOHN BURKINSHAW
From St. James's Hospital, London

A blow on the head, especially if followed by symptoms of concussion, causes anxiety which is born of the knowledge that injury to the brain and other serious complications may occur. A child who attends hospital on account of a head injury is usually admitted for observation for signs of these complications and it is a common practice to x-ray his skull in order to find out whether it has been fractured. The primary object of the present investigation was to determine whether a routine skull x-ray of a child with a recent head injury gives information which helps the doctor either to give a prognosis or to decide on the treatment of his patient. The additional objects of the survey were to assemble information about the age, sex incidence, and causes of head injuries in children.

With these objects in mind I looked through the notes of all the children up to 13 years of age who had been admitted with head injuries into a general hospital in London during the years 1951 to 1956 inclusive. The relevant information was collected from the notes and has been analysed and tabulated. The parents of each patient were then sent a letter requesting their help and were invited to supply the answers to questions relating to the history of the child after discharge from hospital. The answers were scrutinized and the information so provided has been analysed and tabulated.

Criteria

A case was included in the survey if there was a history of a blow on the head and the child showed either some external evidence of the injury (laceration haematoma or abrasion) or had had symptoms suggesting concussion (disturbance of consciousness or memory, drowsiness). Cases were not included where it was clear from the history and appearance of the wound that the injury was merely a simple incised wound and there were no symptoms of concussion. Wounds of the face and eyes only with no symptoms of concussion were also excluded. Some patients had other injuries in addition to the head injury but they were not included unless the head injury satisfied the above criteria.

Classification

The cases were classified according to the severity of the concussion into the following three groups:

Group 1. Slight concussion. Injury to the head with no disturbance of consciousness or memory.

Group 2. Moderate concussion. Injury to the head with any of the following symptoms: Irritability, amnesia or drowsiness, with or without initial loss of consciousness or inaccessibility of less than one hour's duration or, loss of consciousness of less than one hour's duration without other symptoms.

Group 3. Severe concussion. Injury to the head with unconsciousness or inaccessibility for one hour or longer.

Owing to the lack of precise information in the notes about the accident it was necessary in a few instances to make a somewhat arbitrary decision as to the correct classification of the case, and this inevitable weakness of a retrospective survey from case notes must be borne in mind.

Criteria for Admission

Admission of cases to hospital depends upon the assessment of the admitting doctor. Over this period of six years when many different doctors were concerned, each one with his own views and judgment, it is unlikely that there has been true

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uniformity of the criteria for admission into the hospital. Furthermore, it is possible that in London some cases of head injury may have been admitted to other hospitals. This would be most likely in the case of very severe injuries obviously in need of neurosurgical treatment. Such cases cannot be dealt with at St. James's Hospital and would very probably be admitted direct to a neurosurgical unit. For these reasons, therefore, the series under review cannot be taken to represent the whole picture of children with head injuries in this part of London and must be regarded merely as a series of 238 children with head injuries who were considered suitable for admission to a general hospital. The facts disclosed by this survey must therefore be interpreted accordingly. The series consists of 238 children, 182 boys and 56 girls. This gives a ratio of 3·25 boys to 1 girl.

Age and Sex Incidence

The figure shows the incidence by age and sex. The maximum incidence for both sexes is between the ages of 8 and 9 years (26 boys and eight girls) with secondary peaks in boys at 12 to 13 years (25 cases) and 4 to 5 years (15 cases) and in girls at 5 to 6 (6 cases). Table 1 shows the causes of the head injuries in numerical order of frequency in the boys and girls. The ratio of boys to girls injured by each cause is also shown.

Traffic Accidents (60 boys : 18 girls). These include collision with road vehicles of all kinds, including bicycles and cases where the child was in a vehicle which was involved in an accident. They do not include falls from vehicles—notably bicycles when the bicycle or other vehicle itself was

TABLE 1

Cause of Head Injury				Boys	Girls	Ratio Boys Girls	
Traffic accidents	..	..	..	60	18	3·3 :	1
Miscellaneous falls	..	..	..	42	19	2·2 :	1
Fall from height	..		..	29	7	4·1 :	1
Fall off bicycle	..		..	20	2	10 :	1
Hit by moving object	..		..	10	3	3·3 :	1
Fall off moving vehicle	..		..	10	0	10 :	0
Fall down stairs	..		..	5	2	2·5 :	1
Fall off swing	..		..	1	3	0·3 :	1
Fall out of bed	..		..	2	0	2 :	0
Fall in bus	..		..	0	1	0 :	1
Assault	..		..	0	1	0 :	1
Cause uncertain	..		..	3	0	3·0 :	0
Overall ratio { Boys 3·25 Girls 1·0		Total ..		182	56	3·25 :	1

not involved in a collision. Thus if a boy simply falls off his bicycle the injury is classified as 'fall from bicycle' but if he runs into another bicycle or a car it is a 'traffic accident'.

Miscellaneous Falls (42 boys : 19 girls). These include all falls when the child was on the ground or, in the case of a few infants, was being carried and the carrier either fell herself or dropped him. Most of these occurred while at play, and frequently occurred in the school playground.

Falls from Height (29 boys : 7 girls). These include injuries when the child fell to the ground from something above the ground—e.g. out of windows, off walls, trees, tables or ladders.

Falls off Bicycle (20 boys : 2 girls). These falls were much commoner in boys.

Hit by Moving Object (10 boys : 3 girls). This category includes all injuries caused by impact with a moving object other than a vehicle, such as
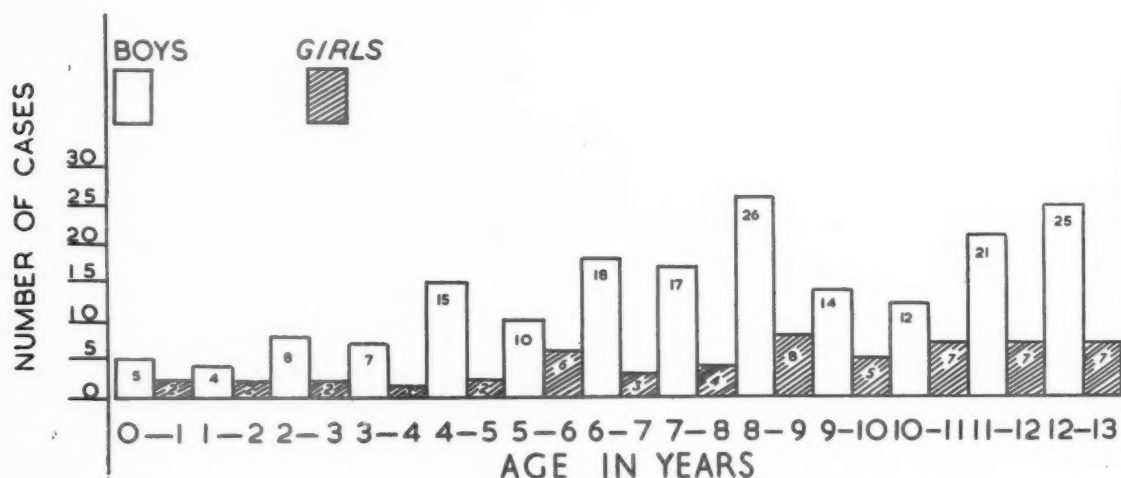
Age and sex incidence.

TABLE 2

CASES CLASSIFIED ACCORDING TO SEVERITY SHOWING PRESENCE OR ABSENCE OF FRACTURE

	Total Cases	No Fracture		Fracture Present		Total X-rayed	Not X-rayed
		Total	% of X-rayed Cases	Total	% of X-rayed Cases		
Severe	17	8	50	8	50	16	1
Moderate	135	96	80	23	20	119	16
Slight	86	52	78	15	22	67	19
Total cases ..	238	156		46		202	36

stones, bricks, falling ladders. The other causes listed in the table do not need further explanation or comment.

Fracture of the Skull in Relation to Severity of Concussion

In Table 2 the cases have been arranged to show the numerical relation between the severity of the concussion and the presence or absence of a fracture of the skull. It will be seen that out of x-rayed cases with severe injury 50% had a fracture of the skull; of x-rayed moderately concussed cases 20% had a fracture; and of those with slight concussion 22% had fractures. A proportion of cases in each category did not have an x-ray of their skull, so that they cannot be included in this particular analysis.

Site of Injury. Table 3 shows the site of the injury to the head in order of frequency and occurrence. It will be seen that right-sided injuries are commoner than left but that the majority of injuries involve the midline and both sides of the head adjacent thereto.

Cases with Complications. When localizing signs were present at the time of the initial clinical assessment, or if the patient's condition deteriorated,

TABLE 3
SITE OF INJURY

	Right	Left	Midline with involvement of both sides	Total
Frontal	23	13	28	64
Occipital	3	4	21	28
Parietal	18	7	2	27
No external signs of injury ..				26
Facial	4	2	17	23
Uncertain				21
Temporal	8	11	0	19
Injuries at two sites ..				13
Injury at one site; fracture at another				11
Bleeding from nose only ..	2	1	0	3
Bleeding from ear only ..	2	1	0	3
	60	39	68	238

or some new symptom or sign made its appearance, the case was considered to have been attended by a complication. Thus, for instance, if some hours after the injury a patient who was conscious, complained of a headache and had hitherto not done so, the headache was regarded as a complication of the injury. If, on the other hand, the patient had complained of a headache as soon after the injury as he was able to express himself, that would not be classed as a complication.

Table 4 shows the cases with complications as

TABLE 4
CASES WITH COMPLICATIONS SHOWING SEVERITY, PRESENCE OF FRACTURE AND SEQUELAE

Case No.	Severity	Fracture	Nature of Complications	Sequelae	Nature of Sequelae
22	Severe	+	Unconscious 18 days; blindness; dementia	+	Dementia; blindness
33	Moderate	+	Meningitis	+	Headaches frequent→occasional
73	Slight	O	Headache	+	Occasional headache
76	Moderate	+	Headache	+	Occasional headache
91	Severe	+	Subarachnoid haemorrhage	O	
96	Slight	O	Headache	+	Occasional headache
99	Slight	+	Headache; vomiting	O	
102	Moderate	O	Diplopia for 5 days	*NR	?
124	Moderate	O	Headache; depression	+	Nerves; occasional headache
140	Severe	+	Lt. hemiparesis; 2 major fits; giddy spells; ocular palsy; attended special school for 10 months	*NR	(Last seen 10 months after injury; well; no fits; no paresis)
142	Severe	+	Died	—	———————
154	Moderate	O	Headache	†NT	———————
193	Moderate	O	Headache	O	
207	Severe	O	Weakness of rt. arm 2 weeks	+	School work worse
215	Moderate	O	Headache	+	Aggressive; headaches frequent→occasional
217	Slight	+	Large occipital subaponeurotic haematoma	O	
235	Moderate	+	Rt. facial weakness 3 weeks	+	Headaches frequent→occasional

* NR = No reply.   † NT = Not traced.

defined above.   The severity of the concussion and
the presence or absence of a fracture of the skull are
shown in each case.

Table 4a shows the relationship between the

TABLE 4A

CASES WITH COMPLICATIONS ACCORDING TO SEVERITY
AND PRESENCE OF FRACTURE

Severity	Number	% of Total in Each Category	With Fracture	No Fracture
Severe ..	5	29	4	1
Moderate	8	5	3	5
Slight ..	4	4	2	2
Totals ..	17		9 (19%)	8 (5%)

severity of the concussion and the presence or
absence of a fracture in these cases with complica-
tions.   It will be seen that nearly half (8/17) of these
patients had no fracture of the skull and that just
over half (9/17) did have a fracture.   The figures in
brackets show the percentage of cases in the three
categories of severity which were attended by
complications.   Of severe injuries 29% were fol-
lowed by complications; the rate with moderate
injuries was 5% and with slight injuries 4%.   Table
4a also shows the number of cases in each grade of
severity in which a fracture was found.   Four out
of five severe cases with complication had a fracture;
three out of eight moderate cases had a fracture and
two out of four of the slight cases had a fracture.

Follow-up

Further information is available about 135 of the
original 238 cases.   This number includes the one
patient who died shortly after the injury (Case 142)
and the one with dementia and amaurosis (Case 22),
who is in a home.   Information about the remain-
ing 133 cases is derived from answers to a question-
naire which was sent to the mothers of all the
patients in the original series.   The minimum period
between the original injury and the date of the reply
was one whole year and the maximum period was
six whole years.

Sequelae.   The symptoms and untoward effects
under consideration were regarded as sequelae if
they occurred after return home from hospital and
they had not been present before the injury
occurred.

Tables 5 and 6 show the incidence of various
sequelae about which information was specifically
sought.   In Table 5 the cases are grouped according
to the presence or absence of a fracture of the skull,
and in Table 6 the grouping is according to the
severity of the concussion.   It will be seen from
these two tables that of cases with fractures 66% had
sequelae and of those with no fracture 49·5% had
sequelae.   Of cases classed as severe (including the
one who died), 61·5% had sequelae; of cases classed
as 'moderate', 51·5% had sequelae and of cases
classed as 'slight' 52% had sequelae.

With the single exception of the one child who is
permanently demented and blind, there is no
surviving child in the follow-up series who is
suffering from sequelae which would be noticeable to
anyone who did not know the child before the
accident, and the majority of symptoms complained
of in the answers might readily be explained away
as coming within the range of normality.

TABLE 5

CASES WITH SEQUELAE ARRANGED ACCORDING TO PRESENCE OR ABSENCE OF FRACTURE (PERCENTAGES TO
NEAREST ½%)

Nature of Sequela	Fracture +	% of Total Cases with Fracture	No Fracture	% of Total Cases without Fracture	Not X-rayed	% of Total Cases not X-rayed	Total Cases
Fits ..	0	0	1	<1	0	0	1
Personality change ..	8	29·5	19	21	3	17·5	30
School work — Better	0	0	10	11	1	6	11
School work — Worse	3	11	10	11	2	12	15
Ataxia, etc. ..	1	3	2	2	0	0	3
Blindness ..	1	3	0	0	0	0	1
Headaches — Occasional	5	18	14	15·5	4	24	23
Headaches — Frequent	4	15	3	3	2	12	9
Headaches — Frequent→occasional	4	15	5	5·5	1	6	10
Died ..	1	3	0	0	0	0	1
Compensation paid	2	7·5	6	6·5	2	12	10
No sequelae ..	9	33	46	50·5	9	53	64
With sequelae	17	66	45	49·5	8	47	70
Total cases ..	27		91		17		

TABLE 6

CASES WITH SEQUELAE ARRANGED ACCORDING TO SEVERITY OF CONCUSSION (PERCENTAGES TO NEAREST ½%)

Nature of Sequela	Slight Injury	% of Total Cases with Slight Injury	Moderate Injury	% of Total Cases with Moderate Injury	Severe Injury	% of Total Cases with Severe Injury	Total Cases
Fits	0	0	1	<1	0	0	1
Personality change	13	25	13	18·5	4	30	30
Better	6	11	4	6	1	7·5	11
School work							
Worse	3	5·5	7	10	5	38	15
Ataxia, etc.	1	2	1	2	1	7·5	3
Blindness	0	0	0	0	1	7·5	1
Occasional	7	13	15	21	1	7·5	23
Headaches							
Frequent	4	7·5	3	4	2	15	9
Frequent→Occasional	3	5·5	7	10	0	0	10
Died	0	0	0	0	1	7·5	1
Compensation paid	7	13	2	3	1	7·5	10
No sequelae	25	48	34	48·5	5	38	64
With sequelae	27	52	36	51·5	7	54	70
Total cases	52		70		13		

Fits. Personality changes were reported in 30 (22%) of the cases in the follow-up series. Table 7

TABLE 7

THE 30 CASES WITH CHANGE OF PERSONALITY

Description	No.
Nervous or highly strung	14
Outbursts of anger and bad temper	6
Sleep difficulties	4
'Phobias' (ladders: heights)	2
Depression	2
Faints	1
'More careful now'	1
Nervous stomach aches	1
Laziness	1
Stuttering	1
Aggressive	1

shows the changes of personality described by those who replied to the questionnaire. In none of the above cases was the change of personality very pronounced and it is, of course, impossible to say whether the change was the result of the injury or of other causes. The only evidence that the injury contributed to these changes is that, according to the parents, they made their appearance shortly after the injuries had been sustained.

School Work. In 11 cases (8%) the parents reported an improvement in school work dating from the return to school after the injury. In 15 (11%) there was a deterioration. The only case who could not receive normal education was Case 22 who is in an institution for mentally defective children and who is also blind as a result of the accident. The parents of some children could not judge the change in intellectual status because they were too young at the time of the accident to attend school. In all cases the change in school work was not very great and in all there was a steady improvement up to the time of the receipt of the questionnaire, the majority of cases having completely regained their previous status.

Ataxia. Parents were questioned specifically about muscular paralysis or weakness and none of the parents who replied to the questions would admit to muscular paralysis in their children, but one child was stated to have lost her sense of balance, one was stated to be more clumsy after the accident, and one to have 'weakness' with no further amplification of the term. The blind child (Case 22) had cortical blindness.

Headaches. Forty-two children (31%) of the follow-up series were reported as having had headaches which dated from the head injury. They have been grouped according to whether the headaches were stated by the parents to be 'frequent' or 'occasional'. No great reliance must be placed upon this classification because no definition of these terms was suggested to the parents, so that the numbers included under these headings are not properly comparable. A third heading is assigned to cases whose headaches were stated to have been frequent at first but which had become only occasional by the time the questionnaire was received. As with the school work and personality change none of these children was seriously handicapped by the headaches, and it is easy to argue that they might well be no more frequent or severe than the headaches felt by any child from time to time.

Compensation. The parents had been asked whether compensation for the injury had been sought

TABLE 8
CASES IN WHOM COMPENSATION WAS PAID

Case No.	Cause of Injury	Severity	Skull Fracture	Other Injuries	Sequelae
36	Fell off swing	Moderate	○	○	Headaches frequent
71	Traffic accident	Slight	○	Leg injury	Nerves; insomnia
82	Traffic accident	Moderate	○	○	Photophobia; nerves; temper; sleep difficulty; headaches
87	Fell off bus	Slight	○	○	○
95	Traffic accident	Slight	+	Abrasions	Nerves; afraid of heights; school work worse
106	Traffic accident	Slight	○ ×	Abrasions	Nerves; frequent headaches
121	Hit by ladder	Slight	+	○	Frequent headaches
165	Traffic accident	Slight	○ ×	Abrasions	○
207	Traffic accident	Severe	○	Abrasions	School work worse
221	Traffic accident	Slight	○	Leg	Occasional headaches

○ × = Not x-rayed.

or received. The object of this was to provide evidence about the frequency of litigation in these cases and also to determine what relation existed between the litigation and the incidence of sequelae. In 10 (7·4%) cases compensation had been paid. Information about these cases is set out in Table 8. In seven out of the 10 patients receiving compensation the head injury had been assessed as 'slight', for two the assessment was 'moderate' and one 'severe'. In six cases there was no fracture of the skull, in two a fracture was present and one was not x-rayed. In one case the compensation was admitted by the parents to have been paid on account of a leg injury sustained at the same time. In seven of the compensated cases the injury was sustained in a traffic accident, one fell off a swing in a public playground, one fell off a moving bus, and one was hit by a falling builder's ladder.

Depressed Fracture. Table 9 shows the four cases in which a diagnosis of depressed fracture was made, either clinically or radiologically. In one case a depressed fracture was missed clinically, and in one it was suspected clinically but not confirmed radiologically. In one case, in spite of the assessment of the injury as 'slight', the patient's depressed fracture was surgically elevated, and the patient had no complication or sequelae. In the patient whose injury was compound and obviously very severe, brain toilet was carried out but the patient died without recovering consciousness. In the remaining

two, treatment was conservative, and of these two patients one had 'frequent-becoming-occasional' headaches as a sequela.

Discussion

Sex Incidence. That boys injure their heads more often than girls is a fact which will not surprise those who are familiar with the ways of children. 'Boys will be boys' is a proverbial truth which must be remembered when planning a programme of investigation into the causes of accidents in children or when preparing any scheme for preventing their occurrence. The restless exploration and aggressiveness of the male are biologically useful to the species in many obvious ways and the tendency of boys to behave as if they were expendable is to the more sedate and careful behaviour of girls, as the reckless mobility of the spermatozoon is to the more sedentary and egocentric habits of the ovum.

Age Incidence. The two age peaks of head injuries shown in the figure provide scope for speculation as to their significance. They are capable of being interpreted as reflecting, in the first peak a phase of development when the child's co-ordination is unequal to his demands upon it, and in the later peak, the intense preoccupation with his activities which makes a boy so heedless of danger.

Cause of Injury. As might be expected traffic accidents accounted for about 33% of the injuries

TABLE 9
CASES WITH DEPRESSED FRACTURE

Case No.	Site of Fracture	Diagnosis		Severity	Treatment	Complications	Sequelae
		Clinical	X-ray				
76	Rt. frontal	○	+	Moderate	Nil	Headache	Occasional headache
92	Rt. parietal	+	+	Slight	Elevation	○	○
102	Lt. frontal	?	○	Slight	Nil	○	○
142	Rt. temporal	+	+	Severe	Brain toilet	Died	—

to both sexes. The only cause which affected girls more often than boys was 'falls off swing', 'fall in bus' and 'assault'. It is perhaps important to know that boys are more liable to be injured by most of the listed causes and not only by traffic accidents, because the chances of a boy being partly responsible for his injury in a traffic accident would appear to be greater than is the case with a girl.

Other Aetiological Factors. Because of lack of the necessary data in the notes it was not possible to go into several other possible aetiological factors which might have been interesting. Among these are the time of the day, the month of the year, the state of the weather, the number in the family, the economic status of the family, the psychological set-up in the home and the emotional or physical state of the child at the time. In planning a future investigation these things might profitably be taken into account.

The Value of Diagnosing a Fractured Skull. The primary object of this investigation was to assess the value, if any, of x-raying the skull in children with head injuries. An x-ray of the skull might possibly be of value if it provided affirmative answers to three questions: (1) Does the finding of a fracture of the skull in the x-ray make necessary any change in the treatment of the case? (2) Does the finding of a fracture of the skull in the x-ray afford more reliable guidance than clinical assessment alone as to the probability of complications? (3) Does the finding of a fracture of the skull in the x-ray afford more reliable guidance than clinical assessment alone as to the probability of sequelae?

With regard to Question 1 relating to immediate treatment, all the cases in this series had been admitted to hospital on account of injuries and all were kept at rest and under close observation. This line of treatment is generally accepted as correct for all cases of head injury and no one would dispute the wisdom of it. If it could be shown that the absence of a fracture of the skull made admission unnecessary, that in itself would fully justify the taking of an x-ray. That such criterion for admission is invalid is shown by Table 4 where it will be seen that of the 17 cases who developed complications nine had a fracture and eight had none.

The Closed Depressed Fracture. Apart from rest and close observation and symptomatic treatment all but two of the cases had no other treatment. The two who were treated surgically both had depressed fractures. One (Case No. 142)

was very severely injured and died after brain toilet in another hospital. The gross and obvious damage to the skull was the indication for this treatment rather than the finding of a depressed fracture, an x-ray finding which merely supported the clinical decision to operate. The second case (No. 92) of depressed fracture had his fracture elevated in accordance with surgical tradition. As has already been pointed out, this child's injury according to the criteria adopted in this investigation was classified as 'slight'. This boy had no untoward symptoms at the time or afterwards. On the other hand one of the four cases with depressed fracture (No. 26) had no surgical treatment and still does complain of occasional headaches. This child's fracture had not been diagnosed clinically. Might he have been saved from these headaches if his depressed fracture had been elevated? If the answer to that question is in the affirmative there can be said to be a case for x-raying all skulls in order to detect missed depressed fractures.

In one case (No. 120) a depressed fracture had been suspected clinically but was not confirmed radiologically. The information about depressed fractures to be had from this investigation is insufficient to justify any conclusion and the writer's experience of the management of such cases is also too meagre for him to venture an opinion. There is wide agreement among leading authorities that operation is advisable for closed depressed fractures of severe degree but for depressed fractures of lesser extent, just the kind that might most easily be missed without an x-ray, a number of authors advise conservative treatment. Dickson Wright and Handfield-Jones (1957) write: 'Simple depressed fractures in children should not be operated upon at first because a great many recover spontaneously. If later elevation of the fragment is deemed necessary all bruising of the soft tissues will have subsided and the danger of infection is thereby lessened'. Browder (1949) writes: 'Instances in which the extent of the depression of the inner table is estimated to be only a few millimetres require only conservative measures unless there is evidence of intracranial complication'. Aird (1957) writes: 'Certain depressed fractures require operation. Most depressed fractures in adults are compound and require operation for that reason; pond fractures in children do not *per se* require operation'.

Wakeley (1952) states: 'In closed depressed fractures in adults always operate; in children if gutter shaped operate; if pond shaped wait for symptoms unless the fracture is a bad one'.

Rowbotham (1949) gives four indications for operating on a closed depressed fracture. (1) When

a patient is unconscious and thought to be suffering from cerebral compression. (2) When there are signs of underlying brain damage. (3) When a fragment of bone is thought to have penetrated the dura. (4) Cosmetic considerations. *Christopher's Textbook of Surgery* (1956) states, 'the majority of patients with simple depressions should be operated on except those having slight depression in the frontal area and small simple depression in the midline and the large venous sinuses'. Bailey and Love (1956) state, 'treatment depends on the extent of the depression and the site of the injury'.

After considering the views expressed by the authorities quoted above one must concede that where there is a clinical suspicion that a depressed fracture may exist it is advisable to x-ray the skull in order to settle the matter. But in a large number of cases which are being discussed the clinical findings were such that even if a depressed fracture were present it would only be a slight 'pond' fracture, of the type that would merely require conservative treatment. It does not seem, therefore, to be necessary to x-ray the skull immediately merely to detect a slight depressed fracture. It should be quite safe to confine x-rays to those cases where there was clinical suspicion of a depression or where surgical intervention was clearly indicated on account of a deterioration in the patient's condition.

The Non-Depressed Fracture. After leaving the troubled waters of the depressed fracture question, one encounters much plainer sailing, and it is beyond dispute that treatment of children with head injuries is exactly the same whether a fracture is demonstrated by the x-ray or not. The chief function of the skull is to protect the brain from damage and this it does remarkably well, though in absorbing the force of a blow, the bone often sustains a fracture. It is a matter of physics that the harder the blow the greater will be the chance of a fracture, but Table 2 shows that, whereas, among severe cases, as defined in this paper, there is a 50/50 chance of the skull having been fractured, the chance of a fracture in cases of moderate or slight severity is approximately the same, namely around 20%.

Question 2 relating to the likelihood of complications can be answered by study of Tables 4 and 4a. These tables show that of the 17 cases which were attended by complications five were severe, eight were moderate and four were slight. Nine had fractures and eight had no fracture and in none of these cases was an x-ray of the skull omitted. Table 4a shows that 29% of severe cases and less

than 10% of the moderate and the slight cases were attended by complications. This table also shows that 19·5% of cases with fractures and 5% of those without fractures were attended by complications. If the incidence of complications in the severe cases is compared with the incidence of complications in the combined slight and moderate cases, the percentages are found to be 29% and 5% respectively. The occurrence of complications can be substantially as accurately forecast, therefore, if judged according to the clinical assessment as according to the presence or absence of a fracture.

The conclusion with regard to Question 2, therefore, is that a skull x-ray is a no better means of foretelling the occurrence of complications to head injury than the clinical assessment of the case alone.

With regard to Question 3, if the cases with sequelae are arranged according to whether a fracture was present or absent, as in Table 5, and then according to severity as in Table 6, a comparison between the two tables will throw some light on the prognostic value of the two methods of classification in regard to the incidence of sequelae.

The three sequelae which occurred in sufficient numbers to merit comparison, are 'Personality Change', 'Changes in School Work' and 'Headaches'. These sequelae were all slight and did not really cause any material disability. Indeed in most cases it would be hard to refute the allegation that the sequelae reported by the parents were in fact quite unrelated to the head injury and were chance occurrences such as might befall any child. It is important to bear in mind that the writer is not attempting to convey the impression that the figures quoted are an accurate numerical account of the incidence of sequelae of head injury. To do this would require a proper control series consisting of children of similar ages who had been in hospital for similar periods of time on account of some disease such as appendicitis. Nevertheless the cases can be used as their own controls to test the relative merits of classification by x-ray and by severity as a means of assessing the likelihood of occurrence of sequelae.

Personality Change. When the cases are arranged according to the presence or absence of a fracture, Table 6 shows that a personality change occurred in 29·5% of cases with fractures and in 21% of cases with no fracture. When classified according to severity, the results are as follows: Severe 30%, moderate 18·5% and slight 25%. If slight and moderate cases are combined, the percentages are: Severe 30%, slight or moderate 21%.

School Work. It was surprising to receive so many replies to the effect that school work had, in the opinion of the parent, actually improved after the injury, but this must be accepted with considerable reserve as to its significance and certainly should not be construed as a possible line of treatment for the mentally sluggish. If the cases showing an improvement are arranged in the same way as was done for cases with a change in personality the results are as follows:

Fracture present	..	0·0%
No fracture	..	11·0%
Severe	.. ..	7·5%
Moderate ..	..	6·0% } Combined 8%
Slight	.. ..	11·0% }

A greater incidence in the slightly injured cases is what might be expected.

The corresponding figures for cases where school work deteriorated are:

Fracture present	..	11·0%
No fracture	..	11·0%
Severe	.. ..	38·0%
Moderate ..	..	10·0% } Combined 8%
Slight	.. ..	5·5% }

Headaches. With regard to headaches the figures are as follows:

(*a*) *Occasional headache*

Fracture present	..	18·0%
No fracture	..	15·5%
Severe	.. ..	7·5%
Moderate ..	..	21·0% } Combined 18%
Slight	.. ..	13·0% }

(*b*) *Frequent headache*

Fracture present	..	15·0%
No fracture	..	3·0%
Severe	.. ..	15·0%
Moderate ..	..	4·0% } Combined 5%
Slight	.. ..	7·5% }

(*c*) *Frequent headaches becoming occasional*

Fracture present	..	15·0%
No fracture	..	5·5%
Severe	.. ..	0·0
Moderate ..	..	10·0% } Combined 8%
Slight	.. ..	5·5% }

The figures as set out above show that with the possible exception of 'occasional headaches' the incidence sequelae of these cases is as well correlated with the severity of the injury as with the presence or absence of a fracture. It is therefore possible to conclude that an x-ray of the skull is no more reliable as a guide to assessing the likelihood of sequelae than the clinical assessment of the case alone.

Conclusion

The facts and figures here presented, though perhaps not statistically conclusive, suggest that apart from the possibility of diagnosing a depressed fracture the routine taking of a skull x-ray in cases of children with head injury serves no useful purpose. It does not help the doctor in his immediate treatment of the case and it is no more reliable than clinical assessment alone as a guide to the likelihood of complications or of sequelae. When a limb bone is fractured the most important consideration is the restoration of the limb's function, which is movement. The limb bones serve as an attachment for the muscles and provide the levers whereby movement of the limb is brought about. When a limb bone is broken abnormal movement may occur at the point of fracture and, if the fragments of the broken bone are not properly aligned, there may be a permanent impairment of the efficiency of the limb. It is therefore important when limb bones are fractured to use x-rays in order to help to bring about as perfect a realignment of the bones as possible. The skull bones, however, are not mainly concerned with the function of movement, and they are so arranged that they are very well splinted by each other and by the overlying aponeuroses and other structures. Their outstanding function is that of a protective armour and as such are designed to be bent and battered to a considerable degree without losing their protective function. There is, therefore, no clinical need to know in every case the precise extent to which the bones have been broken and battered and it is this difference coupled with the knowledge suggested by this investigation which justifies the doctor in omitting to take a routine x-ray of the skull after a head injury and to reserve this investigation for cases for whom it is considered on clinical grounds to be necessary.

The indications for an immediate skull x-ray in children with head injuries appear to be as follows:

(1) In order to obtain evidence that the head has been struck in cases where the suspicion exists but where no external signs of damage to the head can be found.

(2) In order to confirm a clinical suspicion of depressed fracture.

(3) In order to define the extent of damage to the bones in cases where immediate surgical treatment is contemplated.

Many doctors continue, as a routine, to x-ray the skulls of their patients with head injuries although they are by no means convinced of the value of doing so. If asked why they do so they will reply that they do it to provide themselves with 'medico-

legal cover'. Lawyers do not know much about medical practice but they rightly expect a doctor to have acted in accordance with accepted medical practice. If, therefore, doctors always take skull x-rays merely to satisfy the lawyers, one can hardly blame the lawyers for expecting them to continue to do so. It is the doctors' duty to teach the lawyers that when treating a child with a head injury an x-ray of the skull is not always an essential item in the correct management of the case. It is only after they have been taught this lesson that the lawyers will cease to expect a skull x-ray on all occasions.

I wish to thank Mr. Metcalfe and Mr. Thomas for permission to follow up these patients, most of whom were in their care whilst in hospital.

REFERENCES

Aird, I. (1957). *A Companion in Surgical Studies*, 2nd ed., p. 33(, Livingstone, Edinburgh.
Bailey, H. and Love, R. J. McNeill (1956). *A Short Practice of Surgery*, 10th ed., p. 732. Lewis, London.
Browder, J. (1949). In *Injuries of the Brain and Spinal Cord and Their Coverings*, ed. S. Brock, p. 51. Williams and Wilkins, Baltimore.
Coffey, R. J. and Madigan, H. S. (1953). In *Emergency Surgery*, ed. B. J. Ficarra, p. 824. Davis, Philadelphia.
Gurdjian, E. and Webster, J. E. (1956). In *Christopher's Textbook of Surgery*, 6th ed., ed. L. Davis, p. 1370. Saunders, Philadelphia and London.
Rowbotham, G. F. (1949). *Acute Injuries of the Head*, 3rd ed., p. 240. Livingstone, Edinburgh.
Wakeley, C. (ed.) (1952). *Rose and Carless' Manual of Surgery*, 18th ed., Vol. I, p. 607. Baillière, Tindall and Cox, London.
Wright, A. Dickson and Handfield-Jones, R. M. (1957). In *The Essentials of Modern Surgery*, 5th ed., ed. A. M. Handfield-Jones and A. E. Porritt, p. 887. Livingstone, Edinburgh.

THE IMPORTANCE OF ACCIDENT-PRONENESS
IN THE AETIOLOGY OF HEAD INJURIES IN CHILDHOOD*

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The term 'accident-proneness' was originally coined by Farmer and Chambers (1926) to describe a concept arising out of the observations of Greenwood and Woods (1919) and Newbold (1926). These workers had studied the distribution of accidents among factory hands and found that a relatively large proportion of accidents was reported from a relatively small proportion of the population at risk. This undue concentration of accidents could not be explained by chance variations or variations in exposure to danger. It was concluded that certain individuals had some sort of personality trait which rendered them more liable to have accidents. This trait (accident-proneness) seemed to be independent of the environment and constant for the individual from year to year.

Accident-proneness is now also used to denote a somewhat similar concept which has arisen from the psychological study of particular case-histories. Groddeck (1923), Menninger (1936) and others have suggested that many accidents are not entirely fortuitous but are in some way caused by the injured persons themselves. The process is said to be unconscious and motivated by complex desires for self-punishment and death. Flanders Dunbar (1943, 1947) attempted to combine both psychological and statistical approaches to the subject.

The existence of accident-proneness is now widely accepted. There is still, however, a considerable difference of opinion on its place in the aetiology of accidental injuries in general. Some workers (Heinrich, 1941; Dunbar, 1947) regard it of major importance but others (Adelstein, 1952; Schulzinger, 19) think that it is of little significance. A common view, quoted by Schulzinger, is that 'the accident-prone 15% of the population causes 85% of the accidents'. Attempts to predict accident-proneness have not met with much success (Chambers, 1955).

Little work has been done on accident-proneness in childhood. Ackerman and Chidester (1936) presented a case-history of a girl who had repeated accidents. Bakwin and Bakwin (1948) reviewed the subject. Some individual and social comparisons have been made between children who have had one or more accidents and those who have not. Differences have been found, but it is remarkable how small these are. For instance, 'accident-repeaters' have been found to be more aggressive, impulsive and rebellious (Birnbach, 1948), obstinate, impatient, vigorous, hyperactive, rude and highly-strung (Fuller, 1948), but the meaning of such differences is hard to assess. In children under the age of 5 years, Douglas and Blomfield (1958) found little difference in housing conditions, social class or maternal care between accident and control groups; children with two or more accidents were found to have slightly better physical development and mental ability. Langford, Gilder, Wilking, Genn and Sherrill (1953) found no neurological, ophthalmological or intellectual differences between a small group of accident-repeaters and controls. An increased number of accidental injuries has been reported in the families of injured children compared with the families of control groups (Langford *et al.*, 1953; Backett and Johnston, 1959). This has also been recorded in adults (Dunbar, 1943).

The present work was undertaken in an attempt to see whether accident-proneness plays a significant part in the aetiology of head injuries in childhood.

Material

Two series of observations were made. For the first series the case notes were examined of all children with head injuries admitted to Sheffield Children's Hospital between January 1, 1952 and December 31, 1958. Cases were included on the

following criteria: (1) The child's age was 13 years or under (but birth injuries were excluded). (2) The child was admitted to hospital because of the head injury or associated injuries. (3) There was a history of an accident which could have caused a head injury or obvious evidence of, for example, a fractured skull. (4) The child had one or more of the following: coma, stupor, drowsiness, confusion, vomiting, convulsions, lacerations of the head or bleeding from the nose or ear. These features were usually the reasons for the child's admission. Most of the children suffered mild or moderate head injuries, according to Symonds' (1949) classification. Seventeen children (11 boys and six girls) had severe injuries and three of these died.

The second series consisted of 30 patients with head injuries admitted to the same hospital between September 1, 1958 and April 30, 1959. These were seen personally and the parents interviewed. Full past and family histories were taken with special reference to accidental injuries, burns, and poisonings. These patients were matched by sex and age (to the year over the age of 2 years and to the quarter year below that), with 30 other patients admitted to the same wards during the same period of time. This control group was made up of acute medical cases, since closed head injuries are admitted to medical wards in this hospital. Eighteen of these children had acute infections (eight of the respiratory tract), three had rheumatic fever, two had anaphylactoid purpura, two chorea and five had other miscellaneous conditions. Similar histories were taken from the parents of these children. The two series overlap to some extent.

This hospital is a general children's hospital serving Sheffield and the surrounding districts. The great majority of the patients came from Sheffield itself.

First Series

Sex and Age. There were 1,180 cases of head injury in the first series of whom 825 were boys and 355 were girls. This is a ratio of 2·3 boys to one girl (Table 1). At all ages there were more boys with head injuries than girls. The number of boys and girls at each year of age in the general population of Sheffield is known from the census of 1951 (Registrar-General, 1951). Using these figures, it can be said that the excess of boys with head injuries is not significant ($\chi^2 = 2 \cdot 75$; n = 1; $0 \cdot 2 > p > 0 \cdot 1$) under the age of a year. It becomes significant ($\chi^2 = 3 \cdot 71$; n = 1; $p \simeq 0 \cdot 05$) for the first 2 years of life and highly significant ($\chi^2 = 6 \cdot 63$; n = 1; $p = 0 \cdot 01$) if the first 3 years of life are taken

TABLE 1

AGE AND SEX DISTRIBUTION OF THE CASES OF HEAD INJURY

Age in years	Boys	Girls	Totals	No. of boys per girl
Under 1	29	18	47	1·6
1–	51	34	85	1·5
2–	52	36	88	1·4
3–	62	38	100	1·6
4–	66	37	103	1·8
5–	69	34	103	2·0
6–	86	31	117	2·8
7–	86	30	116	2·8
8–	82	29	111	2·8
9–	82	21	103	3·9
10–	56	23	79	2·4
11–	42	8	50	5·3
12–	36	11	47	3·3
13–	26	5	31	5·2
	825	355	1,180	2·3

together. In general, after the age of 2 years, the ratio of boys to girls steadily increased with age.

The age and sex distribution of the cases are shown in Tables 1 and 2 and Fig. 1. It can be seen that the total number of cases rose steadily from the youngest age groups to a plateau at 6 to 8 years and thereafter declined. There were nearly four times as many cases at the age of 6, 7, or 8 years than at the age of 13 years.

There was a marked difference in the age distribution of head injuries in boys and girls. The peak frequency for girls was at the age of 3 years, followed by a steady decline with each older age group. The peak frequency for boys, on the other hand, was at the age of 6 to 9 years, and the numbers fell rapidly after that.

Month of the Year. Fig. 2 shows the monthly incidence of cases of head injury for each year of the survey. More cases regularly occurred in the summer than in the winter months. The whole series is summated for one year in Fig. 3, together with the distribution of cases according to sex and age group. Seasonal variations were most marked in the numbers of boys in the 0 to 4, and 5 to 9 year old groups.

TABLE 2

DISTRIBUTION OF CASES OF HEAD INJURY BY SEX AND AGE GROUPS

Age Group (years)	Boys	%	Girls	%	Totals	%	No. of Boys per Girl
0–4	260	22	164	14	423	36	1·6
5–9	405	34	145	13	550	47	2·8
10–13	160	14	47	3	207	17	3·4
	825	70	355	30	1,180	100	2·3
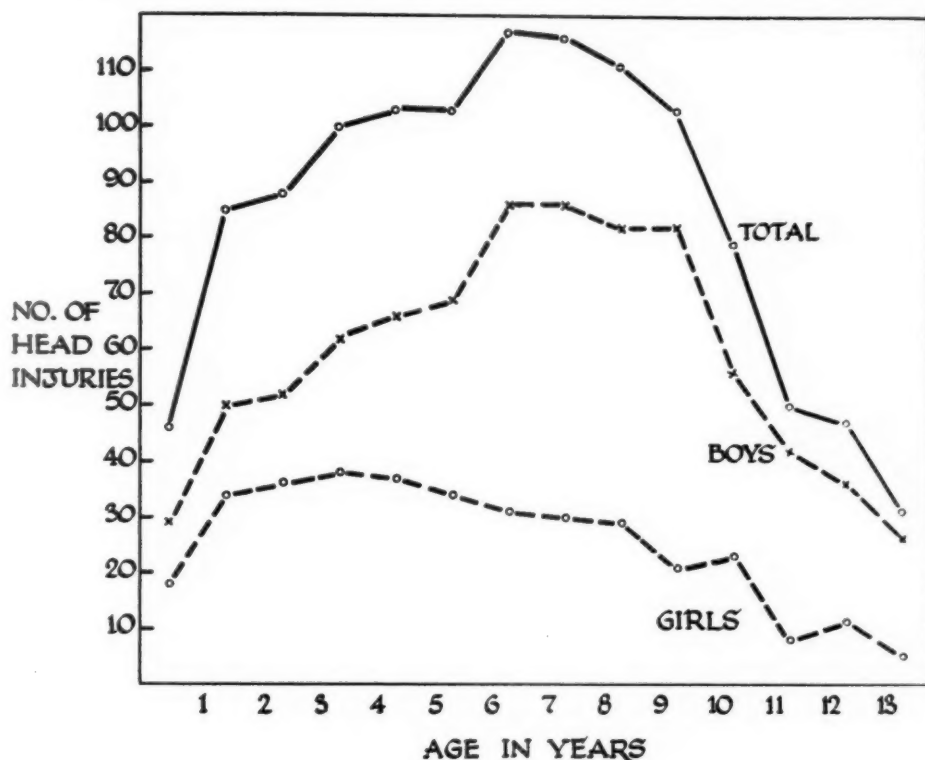
FIG. 1.—Age and sex distribution of all the cases of head injury from the first series.
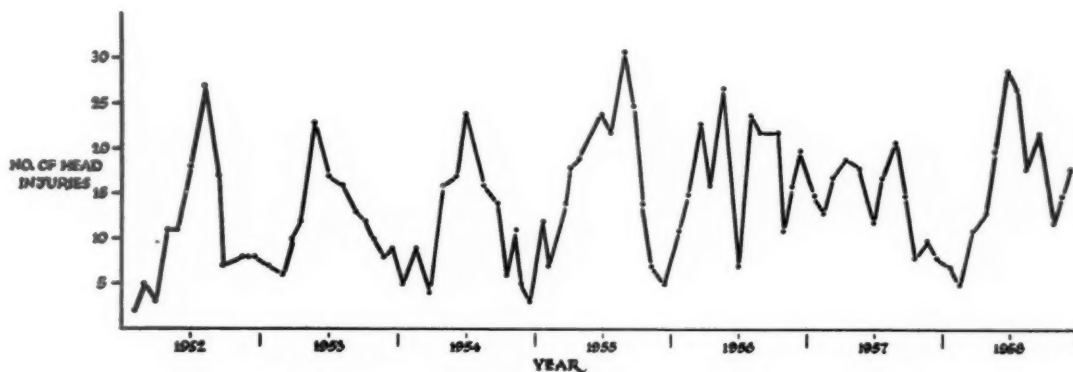
FIG. 2.—Monthly incidence of the first series of head injuries for each year of the survey.

Day of the Week. Fig. 4 shows the cases distributed according to the day of the week on which the accident occurred. There were only slight daily variations and the differences are not significant ($\chi^2 = 4\cdot15$; $n = 6$; $0\cdot7 > p > 0\cdot5$). The ratio of boys to girls altered very little from day to day in the series as a whole and in the different age groups.

Time of Day. There was enough information in the notes to time the accident to the nearest hour in 649 cases (Fig. 5). There were two peak periods, one at midday and another larger one at 5 to 6 p.m. Each age group showed the same sort of pattern but it was least marked in the 10 to 13 year old group and most obvious in the 5 to 9 year old group.
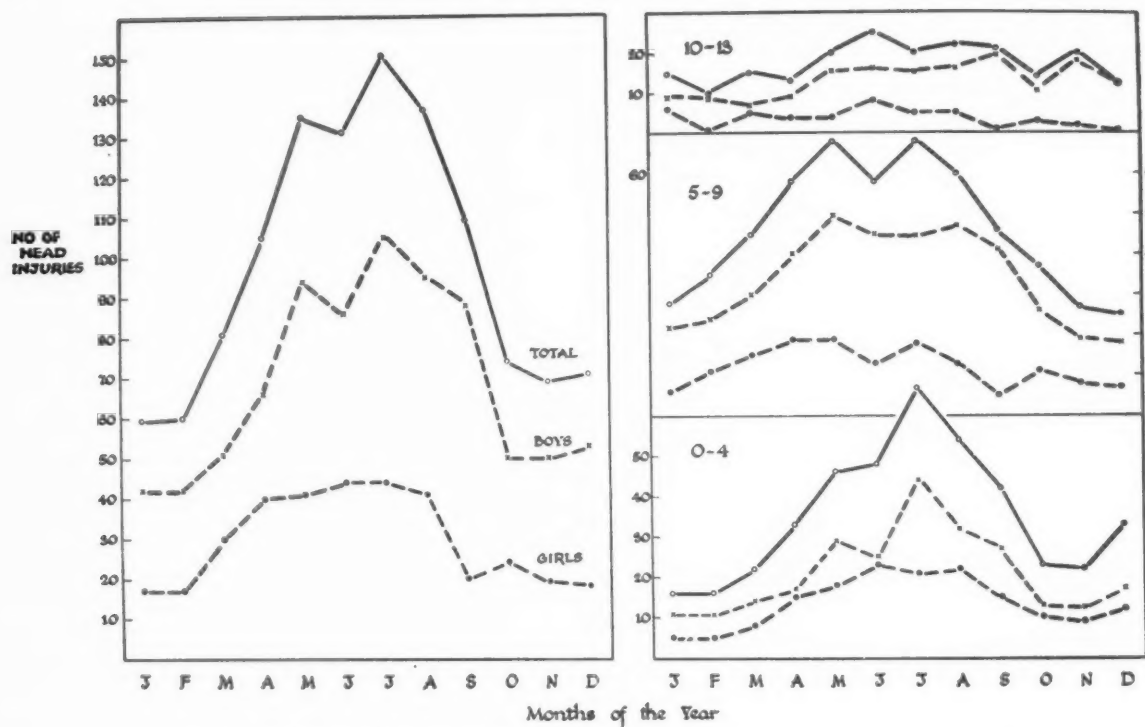
FIG. 3.—Distribution of the first series of head injuries by month of the year, sex and age-group.
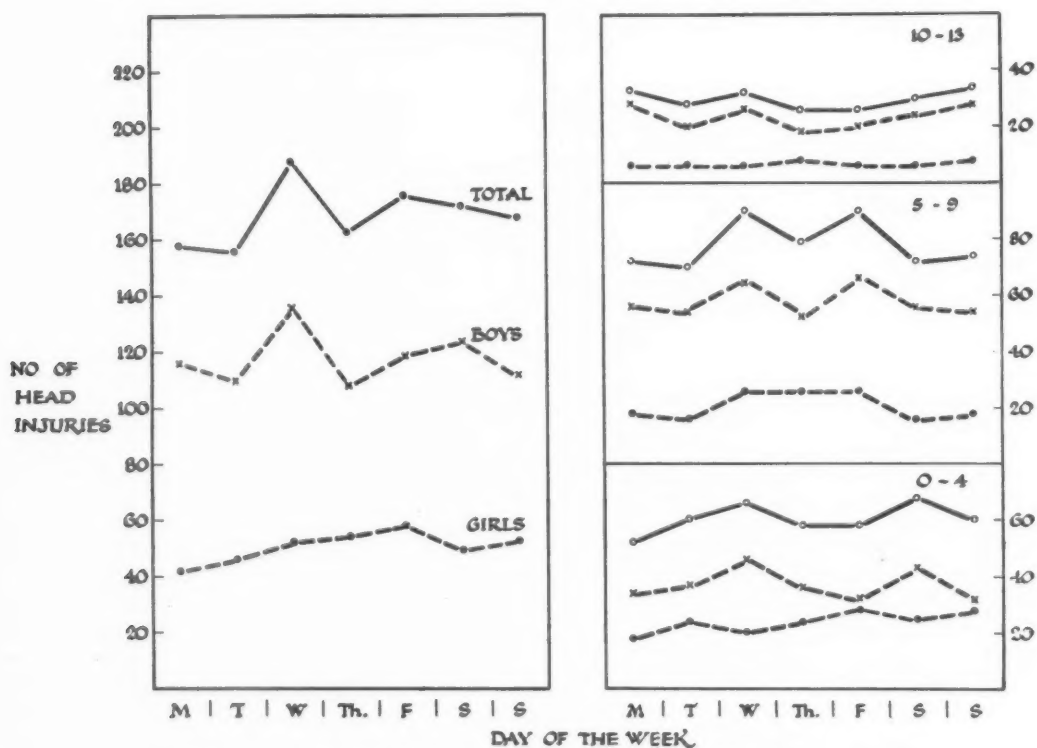
FIG. 4.—Distribution of the first series of head injuries by day of the week, sex and age-group.
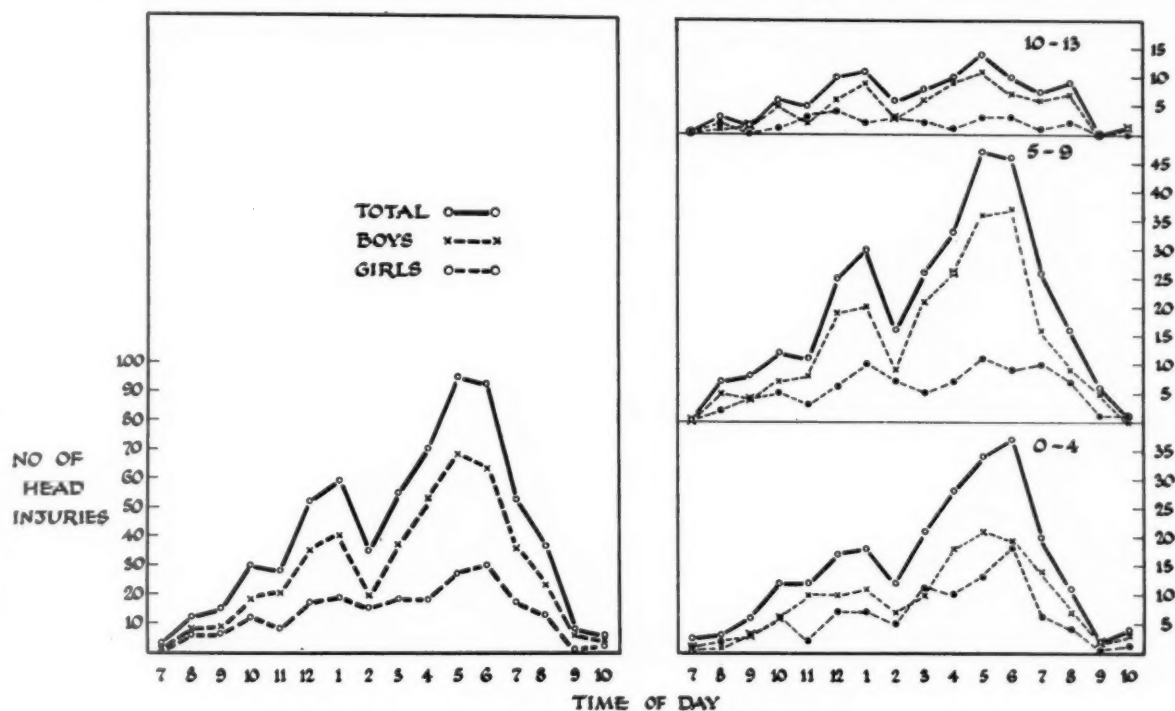
FIG. 5.—Distribution of 649 cases of head injury from the first series by time of day, sex and age-group.
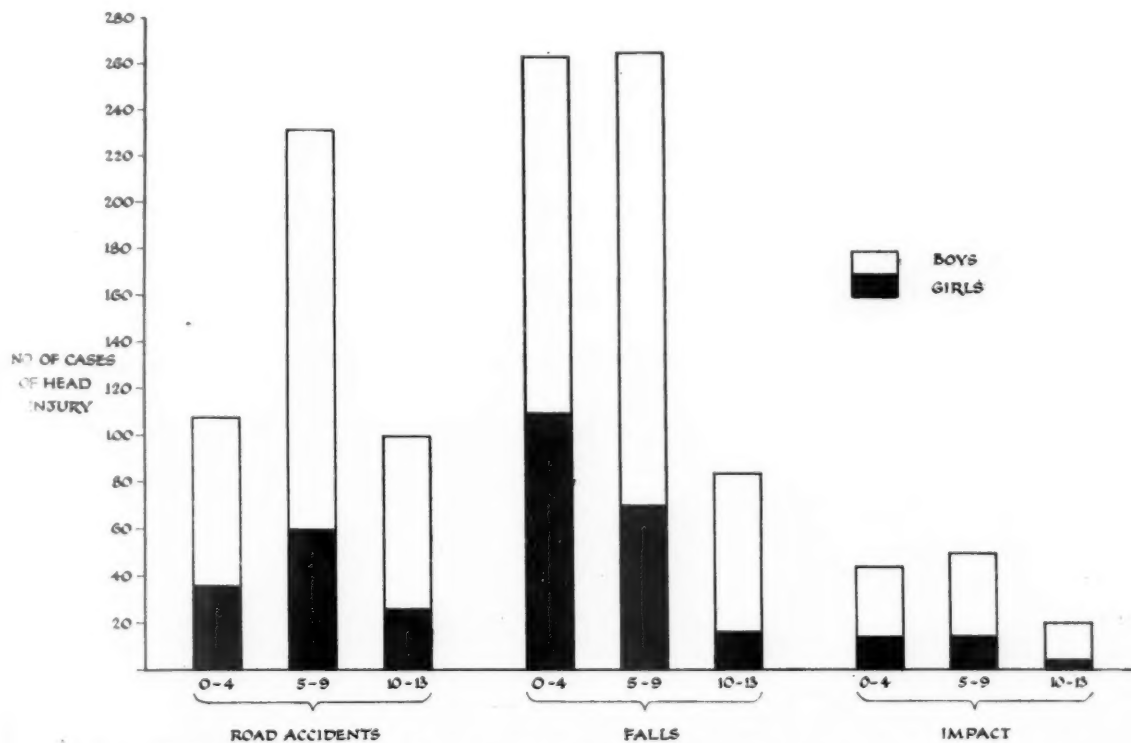
FIG. 6.—Distribution of 1,172 cases of head injury from the first series by type of accident, sex and age-group.

The peak frequencies in this latter group were almost entirely made up of boys, whereas the peak frequencies in the 0 to 4 year old group were made up of both boys and girls.

Type of Accident. Precise details of the accident causing the injury were seldom available. There was enough information, however, to classify the accidents into three main types. All accidents involving a moving vehicle were described as road accidents. Falls included falls from a height and falls on the child's own level. The term 'impact' was used for those cases in which the child was struck by or ran into an object. The results are shown in Fig. 6.

Falls were the largest category of accident. Falls were as common in the 0 to 4 year old group as in the 5 to 9 year old group. The 5 to 9 year old suffered more road accidents. There were more boys than girls in each age group of each type of accident.

Accident Repetition. The 1,180 cases were distributed among 1,155 patients. Nineteen children between them had 44 head injuries (Table 3). Put in another way, $1 \cdot 6\%$ of the children suffered $3 \cdot 7\%$ of the head injuries.

Fifteen of these accident-repeaters were boys and four were girls. This sex ratio is not significantly different ($\chi^2 = 0 \cdot 37$; n = 1; $0 \cdot 7 > p > 0 \cdot 5$) from the rest of the series. At the time of their last injury, four were in the 0 to 4 year old group, 13 were in the 5 to 9 year old group and two were in the 10 to 13 year old group. None of these children sustained a severe injury. Thirty-two of the 44 accidents were falls, seven were road accidents and five were due to impact. This distribution is significantly different from the rest of the series ($\chi^2 = 7 \cdot 42$; n = 2; $0 \cdot 05 > p > 0 \cdot 02$) and indicates that repeated head injuries were more often due to falls than to road accidents or impact.

In addition to these 19 children, 57 children had had one or more accidental injuries in the past requiring medical attention (lacerations, known and suspected fractures, poisoning, etc.). In all, the n, a total of 76 children ($6 \cdot 6\%$) had a past history of accidents at the time of their head injury. Sixty-three of these were boys and 13 were girls. This excess of boys is significant ($\chi^2 = 5 \cdot 91$; n = 1; $0 \cdot 02 > p > 0 \cdot 01$) compared with the rest of the series. Sixty-five children had a past history of one accident, eight of two accidents and three of three accidents.

Second Series

The past and family history of children with head injuries was studied more closely for two reasons. In the first place it seemed likely that the past histories in the case notes of the first series were inadequate. In the second place, because of the observations of Langford *et al.* (1953) and Backett and Johnston (1959), a greater incidence of accidental injuries was expected in the families of these children than in a control group.

The patients of the control group were chosen to match the age and sex of the patients with head injuries. The 60 children of these two groups were called the index cases. It was found in retrospect that the two groups were very similar with regard to a number of other general features (Table 4). There were few differences in the informant's kinship to the index cases, the informant's own estimates of their housing conditions or the social class of the children in each group as judged by the occupation of the father.

TABLE 3

DISTRIBUTION OF 1,180 CASES OF HEAD INJURY AMONG 1,155 PATIENTS

No. of Head Injuries	Number of Children	Cases
1	1,136	1,136
2	14	28
3	4	12
4	1	4
Totals	1,155	1,180

TABLE 4

COMPARISON OF AGE, SEX, INFORMANTS, HOUSING AND SOCIAL CLASS OF ACCIDENT AND CONTROL GROUPS OF THE SECOND SERIES

	Head Injury Group	Control Group	Totals
Sex:			
Boys	20	20	40
Girls	10	10	20
Age group:			
0–4 years	9	9	18
5–9 years	13	13	26
10–13 years	8	8	16
Informants:			
Both parents	14	14	28
Mother	14	12	26
Father	2	3	5
Sister	0	1	1
Housing:			
Unsatisfactory	6	5	11
Satisfactory	24	25	49
Social class:			
I and II	3	8	11
III	15	12	27
IV and V	12	10	22

TABLE 5

COMPARISON OF PAST AND FAMILY HISTORY OF INJURIES IN ACCIDENT AND CONTROL GROUPS OF THE SECOND SERIES

	Head Injury Group	Control Group	Total	Value of χ^2	Value of p
1. Index cases:					
No. of individuals	30	30	60	—	—
No. with past history of injury	13	10	23	0·16	0·7–0·5
No. of injuries incurred	19	18	37	—	—
2. Siblings:					
No. of individuals	66	44	110	4·11	0·05–0·02
No. with past history of injury	6	9	15	2·04	0·2–0·1
No. of injuries incurred	8	10	18	1·46	0·3–0·2
3. Parents:					
No. of individuals	60	60	120	—	—
No. with past history of injury	31	26	57	0·28	0·7–0·5
No. of injuries incurred	46	39	85	0·42	0·7–0·5
4. Close family: (2 and 3)					
No. of individuals	126	104	230	1·92	0·2–0·1
No. with past history of injury	37	35	72	0·33	0·7–0·5
No. of injuries incurred	54	49	103	0·08	0·8–0·7
5. Remote family: (grandparents, parents' siblings, first cousins)					
No. of individuals	528	440	968	5·06	0·05–0·02
No. with past history of injury	42	40	82	0·24	0·7–0·5
No. of injuries incurred	57	50	107	0·02	0·9–0·8
6. Whole family: (1+4+5)					
No. of individuals	684	574	1,258	9·44	>0·01
No. with past history of injury	92	85	177	0·34	0·7–0·5
No. of injuries incurred	130	117	247	0·24	0·7–0·5

Results

The results are summarized in Table 5. Thirteen of the children with head injuries had a past history of injury, compared with 10 in the control group. The 13 children in the head injury group had had 19 injuries between them, and the 10 children in the control group had had 18 injuries. Neither of these differences is significant. Similar comparisons were made between the siblings of the index cases, their parents, their more distant relatives and combinations of these groups. No significant differences were found in the incidence of past injuries. There were significantly more siblings and relatives in the families of the head injury group.

Over a third of the 60 index children had a past history of injury. Twenty of these children were boys and three were girls. This is significantly ($\chi^2 = 5·38$; n = 1; p $\simeq$ 0·02) more boys than would be expected from the sex ratio of the rest of the series. There was a history of injury in nearly half of the parents, roughly a seventh of the siblings and a twelfth of the remote family.

Discussion

The incidence of head injuries in this series was found to vary with four main factors: sex, age, the month of the year and the time of day. The most important of these appeared to be the child's sex.

There were consistently more boys than girls in all situations that were examined. More boys had head injuries at each year of age, in every month of the year, on each day of the week and at each hour of the day. More boys suffered each particular type of accident. More boys had severe head injuries, repeated head injuries and a past history of other accidental injuries.

The ratio of boys to girls in the first series was 2·3 to 1. This might conceivably be due to an excess of boys over girls in the general population. In Sheffield, however, the ratio of boys to girls is only 1·05 to 1 (Registrar-General, 1951), so that this can only account for a small fraction of the preponderance of boys with head injuries. Others have reported a similar sex incidence (Beekman, 1928; Ireland, 1932; Fabian and Bender, 1947; Rowbotham, Maciver, Dickson and Bousfield, 1954; Harris, 1957).

More boys had a past history of accidental injury than girls. This suggests that, in general, boys are more prone or liable to accidents than girls. This is borne out by mortality figures (van den Berg, 1957), hospital accident series (Simson, 1956), surveys of home accidents (Dennis and Kaiser, 1954) and other community studies (Jacobziner, 1955; Rice, Starbuck and Reed, 1956). This is not necessarily true for every type of injury because, for example, burns are commoner in girls

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than in boys (Colebrook, Colebrook, Bull and Jackson, 1956).

A boy's relative proneness to head injury seems to vary with age. The ratio of boys to girls with head injuries steadily increased after the age of 2 years. However, as in other series (Ireland, 1932; Rowbotham *et al.*, 1954; Harris, 1957), the maximum incidence of cases was in the middle years of childhood. These two factors offset one another so that the commonest age for head injuries in boys was 5 to 9 years.

Seasonal variations in the incidence of fatal (van den Berg, 1957; Kanellakis, 1958) and non-fatal (DeCosse, 1953; Jacobziner, 1955) childhood accidents are well recognized. The greatest danger is in the summer months. The present series of head injuries conformed to the same pattern. There were no significant variations in the number of head injuries according to the day of the week, although both DeCosse (1953) and Ehrenpreis (1957) have reported low incidences of accidents in general on Sundays compared with the rest of the week.

Marked variations occurred in the time of day the accident happened. Peak periods were at noon and at 5 to 6 p.m. There were considerable differences between boys and girls and between the age groups in this respect. Most of the variation was due to variations in the numbers of boys. Corresponding variations did occur in the numbers of girls but these were small and only proportional in the 0 to 4 year old group. The most marked variations occurred in the numbers of 5 to 9 year old boys. Similar hourly variations have been noted for childhood accidents in general (DeCosse, 1953; Ehrenpreis, 1957). Ehrenpreis states that, in Sweden, the peak periods correspond to the hours before the main mealtimes and he suggests that more accidents happen because the children are more irritable, hungry and less well supervised. It would be of great interest, in this country, to see if the hourly accident pattern changed if milk were given out in schools in the afternoons instead of in the mornings.

Only a small proportion (1·6%) of children were represented more than once in the first series of head injuries. This, by itself, suggests that accident-proneness was of no great aetiological importance. On the other hand, it might be expected that accident-proneness would express itself differently at different ages. Affected children who have head injuries at the age of 5 to 9 years might have suffered burns, scalds or poisoning earlier in life. If accident-proneness is important in the aetiology of head injuries, one would expect a higher incidence of past injuries in a group of children with head injuries

than in controls. This could show itself in two ways. (1) There could be a greater number of children with a past history of injury. (2) Each group could have the same number of children with a past history of injury, but these children could have incurred a greater total number of injuries (i.e. they are accident-repeaters). No evidence of either of these situations was obtained from the second series of patients.

The second series revealed a high incidence of past injuries among children and their parents in both the accident and control groups. It was also found that the children with head injuries came from slightly larger families than the controls. In contrast to Langford *et al.* (1953) and Backett and Johnston (1959), no significant difference was found in the incidence of accidental injuries in the families of the two groups.

In conclusion, apart from increased liability associated with the male sex, no evidence of accident-proneness was discovered. This does not disprove the existence of accident-proneness nor discount its possible importance in the individual case. It does suggest that accident-proneness is of little significance in the aetiology of the great majority of head injuries in childhood.

Adelstein (1952) has critically reviewed the whole subject of accident-proneness. He points out that much of the confusion is semantic and rests on the interpretation of an 'accident'. This can mean death, a major injury, a minor injury or no injury at all but only damage to property (a mishap). It has been assumed (Newbold, 1926; Heinrich, 1941) that these events are closely related and that, for instance, the causes of mishaps or minor injuries are essentially the same as the cause of major injuries and fatalities. This premise is probably inaccurate. For example, in industry, there is only a very low correlation between minor and major injuries (Farmer and Chambers, 1926; Adelstein, 1952). In childhood, the age distribution of non-fatal accidental poisoning is different from that of fatal accidental poisoning (Clements, 1956). There is little correspondence between the causes of accident morbidity and the causes of accident mortality in childhood (Ehrenpreis, 1957). Observations on one type of accidental result (e.g. mishaps, death or a particular injury) do not necessarily apply to another. Adelstein himself found some evidence of accident-proneness in the aetiology of mishaps but little or none in the aetiology of major injuries.

The outstanding objection to the psychological explanations of accident-proneness is that they are based on such dubious evidence. Theories have largely been built up on the patient's view of the

cause of his accident, weeks, months or years after it has happened.

It has been remarked that preoccupation with accident-proneness may well divert attention from other more rewarding aspects of accident causation. These include not only the effects of age, sex and season but also the means whereby a child learns to avoid accidents (Editorial, *British medical Journal*, 1959).

Summary

Two series of children with head injuries were studied. The first series consisted of 1,180 cases admitted to a children's hospital over a period of seven years. The ratio of boys to girls was 2·3 to 1. The maximum incidence of cases was in the middle years of childhood. More cases occurred in the summer than the winter months. There was no significant variation in the number of cases according to the day of the week. Two peak frequencies occurred during the day, one at noon and a larger one at 5 to 6 p.m. Falls were the commonest type of accident. Only 1·6% of the children had more than one head injury; none had more than four.

In the second series, 30 children with head injuries were matched by age and sex with 30 acute medical cases. No difference was found in the incidence of accidental injuries in the past or family histories of these two groups. A third of the children, and half their parents had a history of accidental injury. The children with head injuries came from slightly larger families.

These findings are discussed. No evidence of accident-proneness was found apart from increased liability associated with the male sex.

REFERENCES

Ackerman, N. W. and Chidester, L. (1936). 'Accidental' self-injury in children. *Arch. Pediat.*, 53, 711.
Adelstein, A. M. (1952). Accident proneness: a criticism of the concept based upon an analysis of shunters' accidents. *J. roy. Statist. Soc.*, 115, 354.

Backett, E. M. and Johnston, A. M. (1959). Social patterns of road accidents to children. *Brit. med. J.*, 1 409.
Bakwin, R. M. and Bakwin, H. (1948). Accident proneness. *J. Pediat.*, 32, 749.
Beekman, F. (1928). Head injuries in children. *Ann. Surg.*, 87, 355.
Berg, B. J. van den (1957). Accidents in childhood. Facts as a basis for prevention. Report of an Advisory Group. Wld Hlth Org. Techn. Rep. Ser., No. 118.
Birnbach, S. B. (1948). A comparative study of accident repeater and accident free pupils. Thesis No. 1124, New York University, cited by Bakwin, H. and Bakwin, R. M. (1953), *Clinical Management of Behavior Disorders in Children*, pp. 457-8. Saunders, Philadelphia.
Chambers, E. G. (1955). Psychological tests for accident proneness and industrial proficiency. Med. Res. Council Memo. No. 31. H.M.S.O., London.
Clements, F. W. (1956). Accidental poisoning in childhood. *Med. J. Aust.*, 43, 1, 211.
Colebrook, L., Colebrook, V., Bull, J. P. and Jackson, D. M. (1956). The prevention of burning accidents; a survey of the present position. *Brit. med. J.*, 1, 1379.
DeCosse, J. J. (1953). A study of 212 home accidents. *New Engl. J. Med.*, 248, 837.
Dennis, J. M. and Kaiser, A. D. (1954). Are home accidents in children preventable? *Pediatrics*, 13, 568.
Douglas, J. W. B. and Blomfield, J. M. (1958). *Children under Five*. Allen and Unwin, London.
Dunbar, F. (1943). *Psychomatic Diagnosis*. Hoeber, New York.
—— (1947). *Mind and Body*. Random House, New York.
Editorial (1959). Road accidents in childhood. *Brit. med. J.*, 1, 427.
Ehrenpreis, T. (1957). The prevention of accidents in childhood in Sweden. *Arch. Dis. Childh.*, 32, 495.
Fabian, A. A. and Bender, L. (1947). Head injury in children: predisposing factors. *Amer. J. Orthopsychiat.*, 17, 68.
Farmer, E. and Chambers, E. G. (1926). A psychological study of individual differences in accident rates. Indust. Fatigue Res. Board, Report No. 38. H.M.S.O., London.
Fuller, E. M. (1948). Injury-prone children. *Amer. J. Orthopsychiat.*, 18, 708.
Greenwood, M. and Woods, H. M. (1919). The incidence of industrial accidents upon individuals, with special reference to multiple accidents. Indust. Fatigue Res. Board, Report No. 4. H.M.S.O., London.
Groddeck, G. (1923). *Das Buch vom Es*. Vienna. English edn. (1950). *The Book of the It*, trans. by V. M. E. Collins. Vision, London.
Harris, P. (1957). Head injuries in childhood. *Arch. Dis. Childh.*, 32, 488.
Heinrich, H. W. (1941). *Industrial Accident Prevention*, 2nd ed. McGraw-Hill, New York.
Ireland, J. (1932). Fracture of the skull in children. *Arch. Surg. (Chicago)*, 24, 23.
Jacobziner, H. (1955). Accidents—a major health problem. *J. Pediat.*, 46, 419.
Kanellakis, A. P. (1958). Seasonal swing in mortality in England and Wales. *Brit. J. prev. soc. Med.*, 12, 197.
Langford, W. S., Gilder, R., Wilking, V. N., Genn, M. M. and Sherrill, H. H. (1953). Pilot study of childhood accidents: preliminary report. *Pediatrics*, 11, 405.
Menninger, K. A. (1936). Purposive accidents as an expression of self-destructive tendencies. *Int. J. Psychoanalysis*, 17, 6.
Newbold, E. M. (1926). A contribution to the study of the human factor in the causation of accidents. Indust. Fatigue Res. Board, Report No. 34. H.M.S.O., London.
Registrar-General (1951). *The Census of 1951*. H.M.S.O., London.
Rice, R. G., Starbuck, G. W. and Reed, R. B. (1956). Accidental injuries to children. *New Engl. J. Med.*, 255, 1212.
Rowbotham, G. F., Maciver, I. N., Dickson, J. and Bousfield, M. E. (1954). Analysis of 1,400 cases of acute injury to the head. *Brit. med. J.*, 1, 726.
Schulzinger, M. S. (1954). Accident proneness. *Industr. Med. Surg.*, 23, 151.
Simson, J. C. (1956). A survey of accidents in childhood. *S. Afr. med. J.*, 30, 1030.
Symonds, C. (1949). In *Injuries of the Brain and Spinal Cord and their Coverings*, 3rd. ed. Ed. by S. Brock, p. 71. Baillière, Tindall and Cox, London; Williams and Wilkins, Baltimore.

ABNORMALITIES OF VENTILATORY CAPACITY IN CHILDREN WITH ASTHMA AND BRONCHIECTASIS

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It is now generally accepted that patients with pulmonary diseases frequently suffer from an impairment of ventilatory capacity and that much of their disability is connected with this. A number of methods have been devised to measure the ventilatory capacity, which all depend on measuring the maximum volume which can be ventilated in a given time. It can be done directly by persuading the subject to hyperventilate maximally and measuring the volume of gas expired in 15 sec. or some other part of a minute. This is the direct Maximum Breathing Capacity (M.B.C.)† and it can be performed at a pre-determined rate to a metronome, or at a rate of the subject's own choice. The result is expressed in litres per minute.

A different approach to measuring the same function has been to analyse a single fast maximum expiration against time and take that part of the volume expired in the first second or part of a second, as a measurement of ventilatory capacity. This measurement was introduced about 10 years ago (Tiffeneau, Bousser and Drutel, 1949; Gaensler, 1951) and has since then come into general use. It is termed the Forced Expiratory Volume (F.E.V.) and the time interval referred to is indicated in seconds as a suffix (e.g. $F.E.V._{1.0}$, $F.E.V._{0.75}$).

Kennedy and his colleagues have used the 0.75 sec. volume (Kennedy, 1953) but the 1.0 sec. volume introduced by Tiffeneau *et al.* (1949) has probably become more generally accepted as a standard measurement (Gandevia and Hugh-Jones, 1957).

The original justification for using a timed fraction of the forced vital capacity (F.V.C.) as an estimate of the ventilatory capacity, depended on the concept that this fraction represented that part of the vital capacity which was actually used during hyperventilation, the 'capacité pulmonaire utilisable à

l'effort' of Tiffeneau *et al.* (1949). Thus, if the duration of expiration and inspiration were equal, the one second F.E.V. would be the tidal volume of the Maximum Breathing Capacity performed at a respiratory rate of 30 per min., and the 0.75 sec. F.E.V. would be the tidal volume at a rate of 40 per min. The relationships are more complex than these concepts imply as the times taken for inspiration and expiration are different and the limit of inspiration varies at different rates of breathing (Bernstein and Kazantzis, 1954). In fact, the correct factor by which the $F.E.V._{1.0}$ should be multiplied for prediction of the M.B.C. is 37.5 (Cara, 1953).

In this study the ventilatory capacity is measured in terms of $F.E.V._{1.0}$ and nothing seems to be gained from the practice of converting these values to an indirect M.B.C., except that normal values for the latter are better known. In children, this does not apply and, therefore, in this study values of $F.E.V._{1.0}$ are given unaltered. The Forced Vital Capacity (F.V.C.) is measured at the same time as the $F.E.V._{1.0}$ and from them a ratio termed the F.E.V.% is derived, i.e. $\left(\dfrac{F.E.V.}{F.V.C.} \times 100\right)$.

Very few studies of ventilatory function have been done in children. Kennedy and his colleagues (Kennedy and Thursby-Pelham, 1956; Kennedy, Thursby-Pelham and Oldham, 1957; Thursby-Pelham and Kennedy, 1958), have studied the ventilatory capacity of normal and asthmatic children using the $F.E.V._{0.75}$. (These authors, using a different terminology, refer to this as the Expiratory Flow Rate—E.F.R.) Engström, Karlberg and Kraepelien (1956) have studied the static lung volumes of normal children and Helliesen, Cook, Friedlander and Agathon (1958) the static lung volumes and the mechanical properties of the lungs of normal children. Earlier studies such as that of Stewart (1922) were confined to measurement of the vital capacity.

In initiating an investigation of pulmonary

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function it seemed of importance to find tests which would evoke the cooperation of children and which would measure functions which were, in fact, altered in the chronic pulmonary diseases of childhood. The Forced Expiratory Volume in one second (F.E.V.$_{.1.0}$) had the advantage that it could be measured very simply in a way which is interesting for children.

In a previous investigation (Strang, 1959) 418 healthy schoolchildren were studied and normal standards for F.E.V.$_{.1.0}$, F.V.C. and F.E.V.% obtained. The F.E.V.$_{.1.0}$ was best correlated with standing height, and a regression on the cube of the height with intervals of two standard deviations, derived from this study, provides normal standards for all comparisons in this paper. These are applicable equally to boys and girls.

The present investigation is intended to determine the circumstances in which the Ventilatory Capacity, in terms of the F.E.V.$_{.1.0}$, is lowered, its discrimination as a clinical test and the ways in which the measurement can be used in the management and investigation of bronchitis in childhood.

Clinical Material and Methods

Serial readings of F.E.V.$_{.1.0}$ were made on 59 children with chronic pulmonary diseases. Two groups were examined: 20 with asthma and 39 with bronchiectasis.

Asthma. Twenty children had the syndrome of recurrent dyspnoea, wheezing and cough which is usually termed asthma. All of them had a persistent eosinophilia in the peripheral blood, and none of them had evidence of bronchiectasis. Three of these patients produced purulent sputum from which *H. influenzae* was cultured and eight of the others had mucoid sputum intermittently. This group of patients were examined repeatedly (237 examinations) during the period from July, 1958 to February, 1959 and 14 of them were seen at two-weekly intervals during this period, with the exception of 26 planned examinations which were missed due to holidays, illness and other minor events.

At the beginning of the study general clinical data relating to each child were recorded, including the height, weight and age. At each subsequent visit the following information was also recorded, the clinical signs being classified into four arbitrary grades as follows—(0) Cough absent, no chest signs; (1) Cough present, no chest signs; (2) Cough present, scattered rhonchi audible in some parts of the lungs; (3) Cough present and rhonchi audible in all parts of the lungs. In the group of patients examined at two weekly intervals, the number of attacks of wheezing in the previous 14 days, the number of days since the last attack and the presence or absence of dyspnoea on exertion, were also recorded.

The clinical data were entered on specially prepared forms which provided space for the recording of each of the factors. At each visit the clinical assessment was recorded before the ventilatory measurement was made

and usually the clinical and ventilatory observations were made by two different people working in different rooms.

Bronchiectasis. Thirty-nine patients with the clinical picture of chronic pulmonary infection and expectoration of purulent sputum, were examined. All of these patients had persistent abnormal segmental shadows on plain radiographs of the chest and in 35 the presence of bronchiectasis had been confirmed by bronchography. None of them had eosinophilia. Serial observations were made (209 examinations) but these were less frequent than in the group with asthma as a less marked variation from time was expected.

The following clinical information was recorded for each patient.

(a) The height and weight and age.

(b) The clinical severity in three general grades as follows: (1) No obvious disability other than cough and sputum. (2) Cough and sputum; and in addition, general health interrupted by one or more febrile spells or other episodes of illness each year. (3) Cough and sputum with either dyspnoea or frequent febrile episodes or considerable loss of schooling, so that the child cannot live a normal life at any time.

(c) A note was made of the diffuseness of râles or rhonchi on auscultation of the chest and divided into the following categories of diffuseness. (1) Signs, unilateral and localized. (2) Signs, bilateral and localized (usually basal). (3) Signs disseminated in all parts of the lungs.

A radiological assessment of the extent of the condition was made by examining plain films and bronchograms and making an estimate of the numbers of bronchopulmonary segments containing an abnormal shadow or deformed bronchus. Thirty-two patients had bronchograms which were considered adequate for this count but as the numbers counted on the plain film and on the bronchogram did not always correspond, the larger value in each case was taken as indicating the radiological extent.

The allocation of patients into grades of diffuseness and severity was done by two observers working together with the clinical records of the patients. Some of the ventilatory data had been collected at this time but it was not before them when the assessment was made. The radiological assessment was made with a radiologist who had no knowledge of the ventilatory results.

Testing Procedure. The child was taught how to make maximum fast expirations into a spirometer with a light aluminium bell similar to that described by Bernstein, D'Silva and Mendel (1952), which recorded on a drum revolving at 2 cm. per second. One cm. vertical movement of the bell was equivalent to a volume of 200 ml. so that the recording pen described a time—volume graph of the forced expiration similar to that shown in Fig. 1. After a number of practice attempts, three recordings were made from which mean values of the F.E.V.$_{.1.0}$ and the F.V.C. were calculated. These volumes were corrected to 37° C. and the F.E.V.%, i.e. $\dfrac{\text{F.E.V.}}{\text{F.V.C.}} \times 100$

calculated. In the previous study of normals, 95% of repeated readings of $F.E.V._{1.0}$ were within 3.8% of the individual's mean value.

Each child was examined clinically at the same time as the ventilatory measurements were made. All the children were receiving medical treatment of some kind. The group of 14 children with asthma, who were seen fortnightly, were taking part in a controlled drug trial and each of them was having choline theophyllinate in high dosage during three months of the observation period.

Results

Normal Pattern. Fig. 1 is typical of tracings which were obtained from normal children. The full height of the tracing represents the Forced Vital Capacity (F.V.C.) and the distance between the onset of expiration and the one second point represents the Forced Expiratory Volume in one second ($F.E.V._{1.0}$). In normal children the absolute values of $F.E.V._{1.0}$ and F.V.C. depend on the child's size, but the shape of the curve is constant. This is conveniently expressed as the ratio, $\dfrac{F.E.V.}{F.V.C.} \times 100$ or F.E.V.$\%$. In a study of normal children (Strang, 1959) the mean F.E.V.$\%$ was 85% (S.D. 5.8) in boys and 89% (S.D. 5.4) in girls.
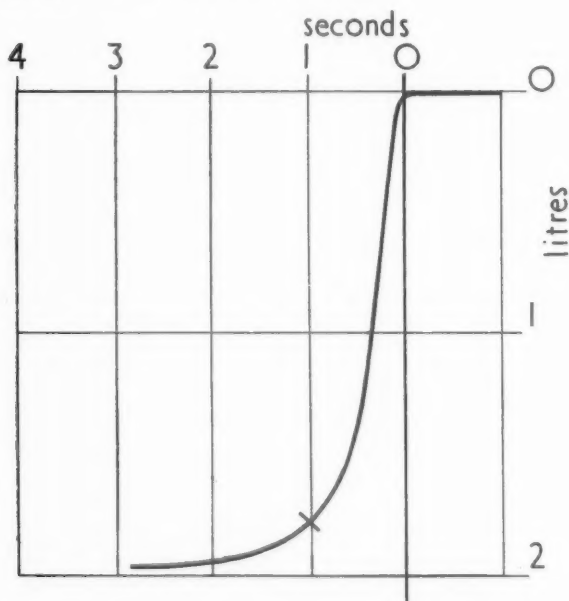

FIG. 1.—Spirometer tracing of maximum forced expiration. Normal child: standing height—53 in.

Abnormal Patterns. The types of abnormal tracing obtained were similar to those described by Thomson and Hugh-Jones (1958) in adult patients. In Fig. 2, three abnormal tracings have been superimposed on that of a normal child, all of the children
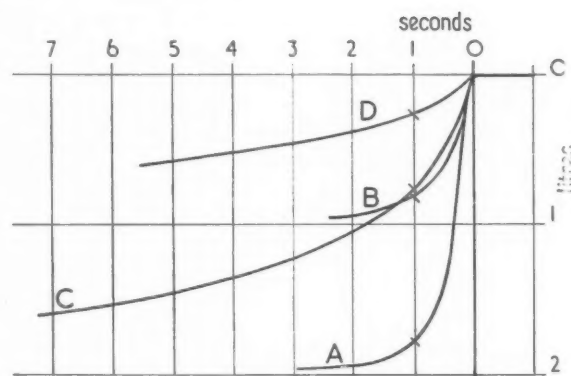
FIG. 2.—Superimposed spirometer tracings of a normal child and three children with chronic pulmonary disease, all 53 in. in height.

being of the same height and, therefore, comparable. A was from a normal child, B from a child with diffuse pulmonary fibrosis due to pulmonary haemosiderosis and C and D from children with asthma. The shape of the curve B was similar to the normal, the $F.E.V._{1.0}$ and F.V.C. being reduced in proportion. This fact is expressed in a normal F.E.V.$\%$. B was of the pattern expected in a restrictive lesion of the lungs or chest wall in which the extent of movement was limited but not its rate. The abnormal shape of curve C was due to a lesion which restricted the rate of movement of the chest, but its total volume only slightly. This was the pattern expected due to bronchial obstruction or diminished elastic recoil of the lungs. The $F.E.V._{1.0}$ was reduced to a much greater degree than the F.V.C. and the F.E.V.$\%$ was much lower than normal. Curve D was a similar pattern but more severe. In this case, the F.V.C. and $F.E.V._{1.0}$ were both diminished but this was more marked for the $F.E.V._{1.0}$ than for the F.V.C.

In each case the $F.E.V._{1.0}$ was a measurement of ventilatory capacity and the F.E.V.$\%$ gave an indication of the cause of the ventilatory impairment.

Results in Children with Asthma. In order to allow comparison between variable clinical factors and the pooled $F.E.V._{1.0}$ results, the latter were converted to a percentage of the mean normal value for the child's height. The pooled results in this group showed a significant discrimination between each of the grades of physical signs (Fig. 3); between the presence and absence of dyspnoea on exertion (Fig. 4) and between whether or not there had been an attack of wheezing in the previous 14 days (Fig. 5); there was no difference between one and more than one attack in this period (Fig. 5) and the number of days since the attack was not apparently
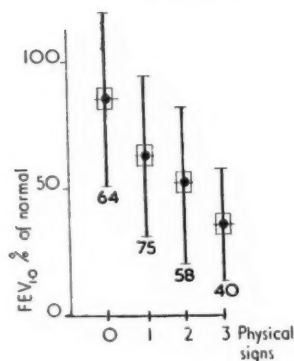
FIG. 3. Asthma. Pooled results of F.E.V. as per cent of normal compared with physical signs on auscultation (20 patients, 237 readings). Black circles indicate means, vertical lines indicate two standard deviations about the means; rectangles indicate two standard errors of the means; numbers refer to number of observations in each group. Where the rectangles do not overlap there is a significant difference between the means.
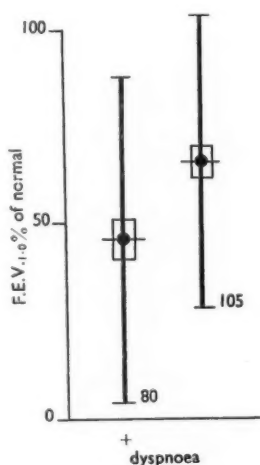
FIG. 4. Asthma. Pooled results of F.E.V. as per cent of normal compared with presence or absence of dyspnoea on exertion at that time. (14 patients, 185 readings.) Symbols and significance as in Fig. 3.
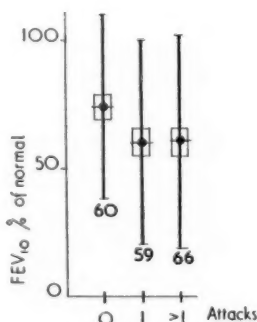
FIG. 5. Asthma. Pooled results of F.E.V. as per cent of normal compared with number of attacks of wheezing in previous 14 days. (14 patients, 185 readings.) Symbols and significance as in Fig. 3.

significant (0-3 days since attack—mean F.E.V. 59%, (n=78): >3 days since attack—mean F.E.V. 65%, (n=47): S.E. of difference between means=5·5).

There was a marked difference between readings of $F.E.V._{1\cdot 0}$ at different times on the same child, the coefficient of variation about the individual means
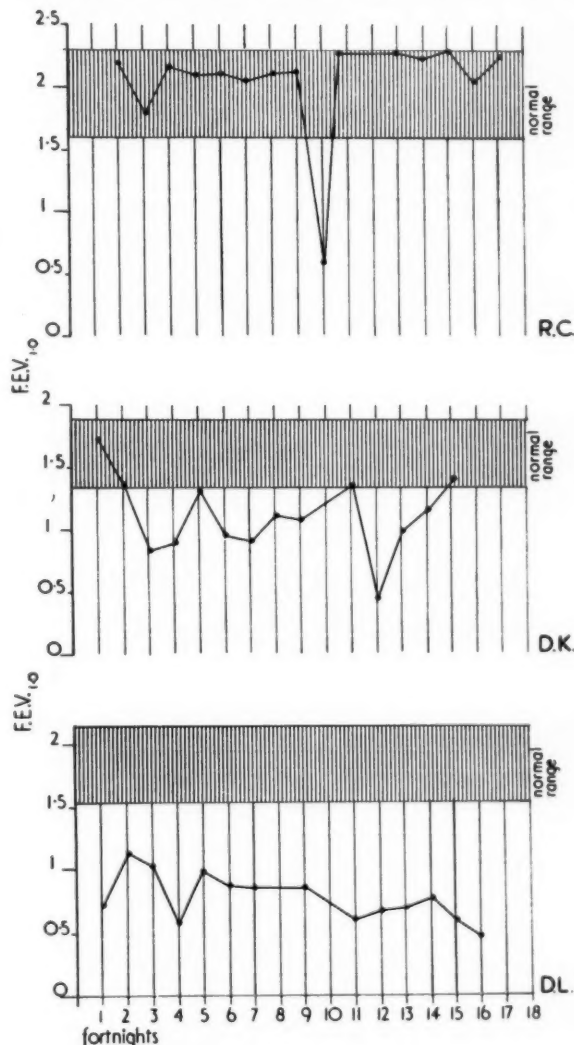
FIG. 6. Asthma. Serial records of F.E.V. in three children.

being 27%. The actual usefulness of the measurement was most evident in serial recordings in individuals such as shown for three children in Fig. 6. The top record is from a child who was in the normal range of ventilatory capacity most of the time but had a short-lived episode of abnormality. The middle record is of a child who was occasionally within the normal range, in this respect, but more frequently below normal. The lowest record is of a
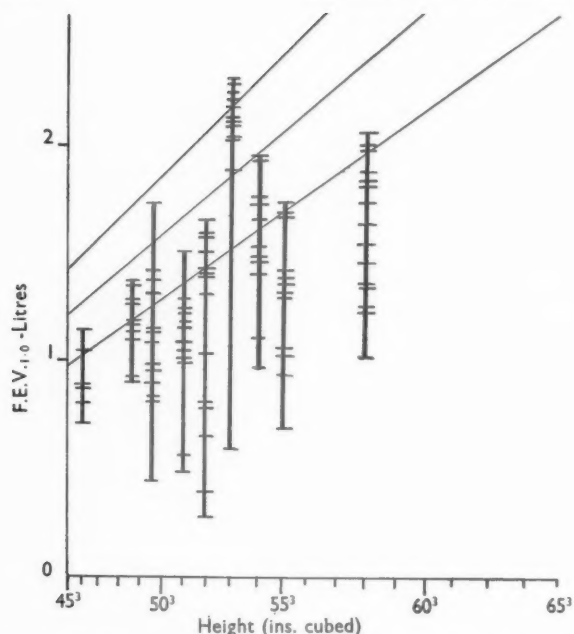
FIG. 7. Asthma. Serial readings of F.E.V. in nine children compared with normal limits, for height. Each child represented as a vertical line and different readings of F.E.V. by short horizontal lines.
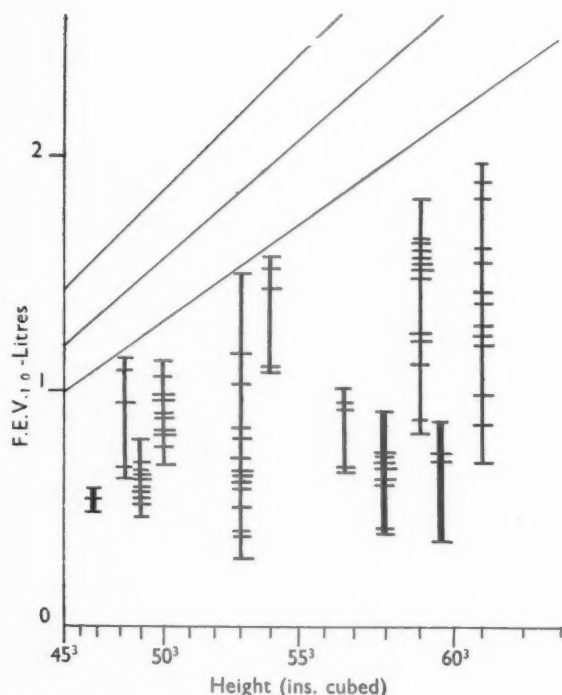
FIG. 8. Asthma. Serial readings of F.E.V. in 11 children compared with normal intervals for height. Each child represented as vertical line and different readings of F.E.V. by short transverse lines. Thick vertical lines represent children with purulent sputum.

child who had a persistently and severely impaired ventilatory capacity throughout the observation period.

The serial records of the 20 children are summarized in Figs. 7 and 8 and compared with the normal limits for height. Nine of these patients were never within the normal during the period of observation (Fig. 8), and particularly severe ventilatory defects were present in the three asthmatic children who also had purulent sputum.

The differences in ventilatory capacity between different children were evidently marked but not readily correlated with clinical data. The mean of the F.E.V.s recorded for each child was compared with the child's height and weight and with the persistence or otherwise of cough. These were the only reasonably permanent clinical characteristics which could be defined in this group.

The mean height was $97 \cdot 8\%$ (S.D. $7 \cdot 95$) of normal.* The mean weight was 83% (S.D. $13 \cdot 8$) of normal and there was no significant correlation between weight (per cent normal) and F.E.V. (per cent normal) ($r = 0 \cdot 184$; $n = 20$). Nine patients had cough on each occasion they were seen and, in 11, cough was absent on one or more occasions, and between these groups the difference in $F.E.V._{\cdot 1 \cdot 0}$ was significant. (Cough persistent mean F.E.V. (per cent normal) $= 49 \cdot 7$. Cough not persistent mean $F.E.V._{\cdot 1 \cdot 0}$ (per cent normal) $= 70 \cdot 08$; $t = 2 \cdot 35$; $p > 0 \cdot 05$.)

Relationship of $F.E.V._{\cdot 1 \cdot 0}$ and F.V.C. ($F.E.V. \%$) in Asthma. Usually a reduction of $F.E.V._{\cdot 1 \cdot 0}$ below normal was proportionately greater than the associated reduction of F.V.C. and this produced tracings similar to C and D in Fig. 2, in which the $F.E.V. \%$ was reduced. These changes were regarded as largely due to bronchial obstruction. In Fig. 9 the relationships of $F.E.V._{\cdot 1 \cdot 0}$ and F.V.C. in these patients is presented. The diagonal line represents the relationship which would exist if the form of the spirometer tracings were normal and in purely restrictive lesions the results could be expected to fall about such a line. The quadratic regression line indicates the trend of the actual data and can be taken to show the changes likely to occur in a severely affected child during treatment or spontaneous improvement. In the low ranges, the $F.E.V._{\cdot 1 \cdot 0}$ increases less markedly than the F.V.C.; they then increase at equal rates and the normal range of F.V.C. is reached before that of the $F.E.V._{\cdot 1 \cdot 0}$ Finally the $F.E.V._{\cdot 1 \cdot 0}$ increases with relatively small change in F.V.C., reaching first the normal range

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* The normal heights and weights were taken as the mean heights and weights for age from the charts prepared by Dr. P. E. Polani for the National Spastics Society.
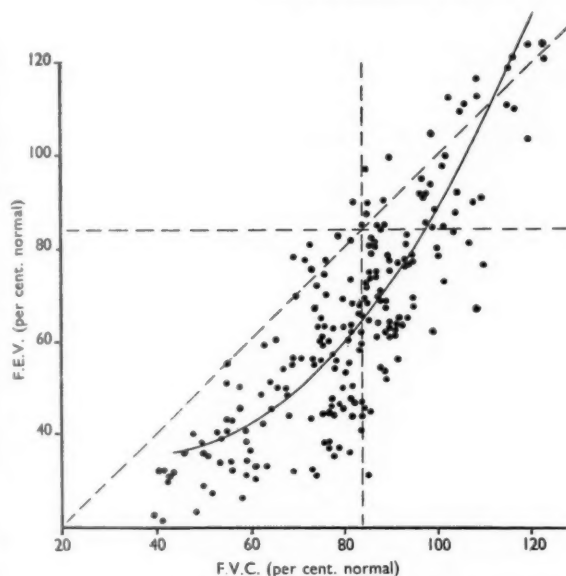
FIG. 9. Asthma. Relationship of F.E.V. as per cent of normal and F.V.C. as per cent of normal (20 patients, 237 readings). Diagonal interrupted line is relationship of F.E.V. and F.V.C. in spirometer tracings of normal shape. Horizontal and vertical interrupted lines show lower limits of normal for F.E.V. and F.V.C. Continuous line is quadratic regression fitted to data. $(F.E.V. = 57\cdot11 - 1\cdot08 \times F.V.C. + 0\cdot0138 \times F.V.C.$: F.E.V. and F.V.C. as per cent of normal for height.)

TABLE 1

BRONCHIECTASIS. COMPARISON OF F.E.V. (PER CENT OF NORMAL) WITH GRADE OF GENERAL CLINICAL SEVERITY

Grade of Severity	No. of Patients	Mean F.E.V. (% normal)	t	p
1	11	72·3 ⎫		
			0·288	>0·05
2	21	70·5 ⎬		
			0·85	>0·05
3	6	63·2 ⎭		

TABLE 2

BRONCHIECTASIS. COMPARISON OF F.E.V. (PER CENT OF NORMAL) WITH DEGREE OF DIFFUSENESS OF SIGNS ON AUSCULTATION

Degree of Diffuseness	No. of Patients	Mean F.E.V. (% normal)	t	p
1	13	74·3		
2	14	73·1 ⎫		
			8·25	<0·05
3	12	57·5 ⎭		

for F.E.V.$_{1\cdot0}$ and finally the normal F.E.V./F.V.C. ratio.

Results in Patients with Bronchiectasis. The variation in F.E.V.$_{1\cdot0}$ at different times in individual patients was less than in children with asthma, the coefficient of variation about the individual means being 12%. Many children had abnormally low F.E.V.s on serial recordings as compared with the normal for height (Fig. 10).

In order to allow comparison with clinical factors, the F.E.V.$_{1\cdot0}$ was expressed as a percentage of the normal for height. Clearly definable clinical variations, from time to time during the observation period, were not very obvious in these patients, so that a comparison of variations in chest signs and similar factors with the pooled data was not relevant. For this reason, comparisons were confined to clinical differences between patients and the mean F.E.V.$_{1\cdot0}$ of each.

The mean height of the group was 97% (S.D. 4·7) of normal. The mean weight was 85·6% (S.D. 10) of normal, but there was no significant correlation between F.E.V.$_{1\cdot0}$ (per cent normal) and weight (per cent normal) $(r = 0\cdot069, n = 39)$. The results in the three grades of general severity were not significantly different (Table 1). The diffuseness of physical signs showed no difference between the

FIG. 10. Bronchiectasis. Serial readings of F.E.V. in 39 children compared with normal limits for height. Each child represented as vertical line and different readings of F.E.V. by short horizontal lines.

first two categories but there was a significantly lower mean in the third category (Table 2). The numbers of affected segments in the radiological

assessment ranged from two to 13 but the correlation with F.E.V.$_{1\cdot0}$ was not significant ($r=0\cdot24$, $n=32$).

F.E.V./F.V.C. Relationship (F.E.V.%) in Bronchiectasis. The relationship of F.E.V.$_{1\cdot0}$ and F.V.C. in these patients was not so obvious as in children with asthma (Fig. 11). In general the trend was similar, reduction of F.E.V.$_{1\cdot0}$ being proportionately greater than the reduction of F.V.C. The degree of this change was less marked, and in some cases the F.E.V.$_{1\cdot0}$ and F.V.C. were reduced in equal proportions.
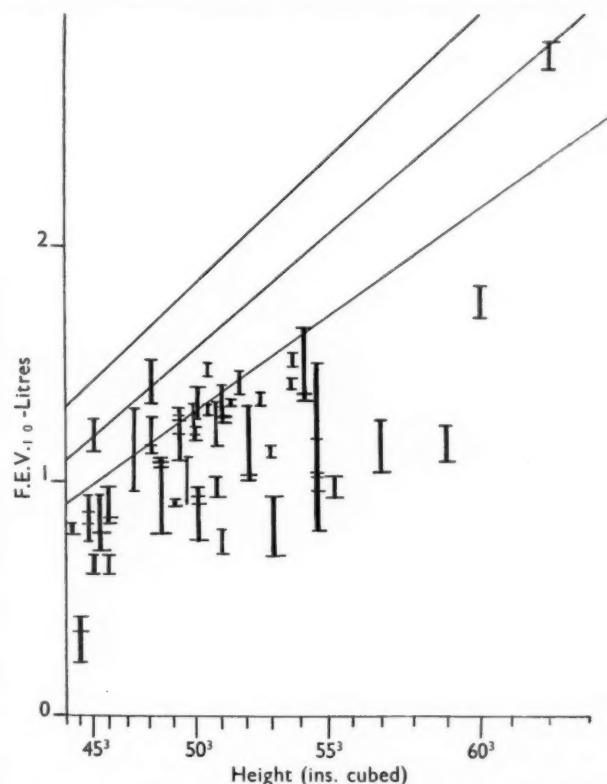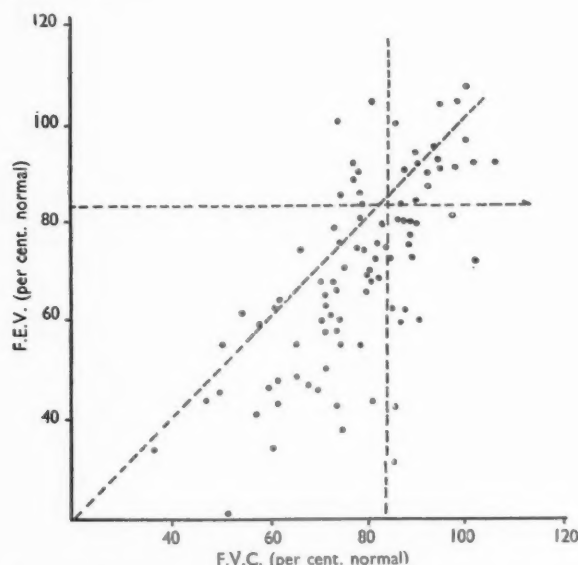

FIG. 11. Bronchiectasis. Relationship of F.E.V. as per cent of normal and F.V.C. as per cent of normal in 39 patients with bronchiectasis (209 readings). Lower limits of normal for F.E.V. and F.V.C., and diagonal indicating normal F.E.V./F.V.C. ratio, as in Fig. 9.

Discussion

Asthma. The severe ventilatory abnormalities in the children with asthma are reasonably closely related to clinical observations, but in the individual case it would be impossible to predict the degree of ventilatory impairment from clinical data, and in particular, serious impairment may be present in the absence of physical signs on auscultation. The usefulness of measuring the F.E.V.$_{1\cdot0}$ is most obvious in the serial records of individual children and the most striking fact about most of these is the relatively continuous nature of the abnormality. Only rarely is it intermittent and the symptoms of overt wheezing arise more often as exacerbations of a chronic condition than from a previously normal ventilatory state.

A number of consequences appear to follow from the concept of asthma as a continuous sub-acute

condition. Treatment with anti-spasmodics or other agents might be expected to achieve optimum results when given continuously three or four times daily over long periods. The results of treatment of this kind would need to be assessed in terms of ventilatory capacity as a degree of impairment will persist after the disappearance of clinical signs. The aim will be to bring the F.E.V.$_{1\cdot0}$ and F.V.C. into the normal limits and during such a development the relationship of F.E.V.$_{1\cdot0}$ and F.V.C. might be expected to follow a trend similar to the regression in Fig. 9. Thomson and Hugh-Jones (1958) have described a similar relationship in adult asthmatics and have pointed out that the normal F.E.V.$_{1\cdot0}$ for a particular patient has not been reached until the normal F.E.V./F.V.C. ratio (F.E.V.%) exists. This is important as the patient is likely to enter the normal range of F.E.V.$_{1\cdot0}$ well before achieving his own particular normal value. Treatment cannot be regarded as wholly successful until a normal F.E.V.% has been achieved.

The persistence of an impaired ventilatory capacity in children over long periods may have a bearing on the natural history of the condition. It cannot be concluded that all of the patients who remained outside the normal limits of ventilatory capacity had permanent pulmonary damage; different treatment, in particular, inhalations of isoprenaline, might have improved some of them. Nevertheless, the possibility exists that a prolonged ventilatory abnormality, which is presumably associated with bronchial obstruction, may contribute to permanent pulmonary damage particularly if additional agents capable of damaging the lung are added to it. In this connexion it may be important that persistent cough was associated with lower values of F.E.V.$_{1\cdot0}$ than when cough was intermittent, and that the three children with persistent cough and purulent sputum were very seriously affected.

Bronchiectasis. The frequency of ventilatory impairment in children with bronchiectasis was greater than expected. These abnormalities are probably due to factors causing increased stiffness of the lungs such as fibrosis and oedema, and also to bronchial obstruction, the latter being more important. Different tests would be necessary to elucidate these factors further.

Whatever the exact cause of the mechanical disorders of ventilation, they are likely to be due to a diffuse process rather than to localized bronchiectasis. The clinical counterpart of ventilatory impairment is not very obvious except in the case of diffuse signs on auscultation. Morbid anatomical

studies including those of Allison, Gordon and Zinnemann (1943) and Whitwell (1952) have shown that the disease may be extremely diffuse and may involve areas which appear normal on broncho-graphy. It has also been known for a long time that patients frequently have persistent cough and sputum following the apparently complete resection of bronchiectatic areas. There is obviously a need for a study which includes pre-operative and post-operative ventilatory measurements, but it seems likely that many children with bronchiectasis may have a diffuse bronchial damage or bronchitis, and in so far as measurement of $F.E.V._{1\cdot0}$ and $F.E.V.\%$ may show this, it should enable detection of children unlikely to benefit from surgical resection.

Field (1949), in a study of bronchiectasis in children, claimed that 33% of children had attacks of wheezing similar to asthma. This observation has not been confirmed in this centre and this may be due to differences in material or in terminology. The presence of impaired ventilatory capacity, due in part to bronchial obstruction, could lead to wheezing in certain circumstances, so that the present finding narrows the difference between our observations and those of Field (1949) to one of degree. Measurement of $F.E.V._{1\cdot0}$ should place the phenomenon on a quantitative basis, thus allowing exact comparisons.

Summary

Measurements of ventilatory capacity, in terms of the $F.E.V._{1\cdot0}$ reveal persistent abnormalities in children with asthma and bronchiectasis. They appear to provide an objective means of assessing an important aspect of these conditions which cannot be accurately assessed on clinical examination.

Measurements of this kind seem readily applicable to assessing the natural course of these diseases and the effects of treatment.

REFERENCES

Allison, P. R., Gordon, J. and Zinnemann, K. (1943). Incidence and significance of *H. influenzae* in chronic bronchiectasis. *J. Path. Bact.*, **55**, 465.
Bernstein, L. and Kazantzis, G. (1954). The relation between the fast vital capacity curves and the maximum breathing capacity. *Thorax*, **9**, 326.
——, D'Silva, J. L. and Mendel, D. (1952). The effect of the rate of breathing on the maximum breathing capacity determined with a new spirometer. *Thorax*, **7**, 255.
Cara, M. (1953). Bases physiques pour un essai de mécanique ventilatoire avec application à la cinésithérapie. *Poumon*, **9**, 371.
Engström, I., Karlberg, P. and Kraepelien, S. (1956). Respiratory studies in children. I. Lung volumes in healthy children 6–14 years of age. *Acta paediat.*, **45**, 277.
Field, C. E. (1949). Bronchiectasis in childhood; clinical survey of 160 cases. *Pediatrics*, **4**, 21.
Gaensler, E. A. (1951). Analysis of the ventilatory defect by timed capacity measurements. *Amer. Rev. Tuberc.*, **64**, 256.
Gandevia, B. and Hugh-Jones, P. (1957). Terminology for measurements of ventilatory capacity; a report to the Thoracic Society. *Thorax*, **12**, 290.
Helliesen, P. J., Cook, C. D., Friedlander, L. and Agathon, S. (1958). Studies of respiratory physiology in children. I. Mechanics of respiration and lung volumes in 85 normal children 5–17 years of age. *Pediatrics*, **22**, 80.
Kennedy, M. C. S. (1953). A practical measure of the maximum ventilatory capacity in health and disease. *Thorax*, **8**, 73.
—— and Thursby-Pelham, D. C. (1956). Cortisone in treatment of children with chronic asthma. *Brit. med. J.*, **1**, 1511.
——, —— and Oldham, P. D. (1957). Pulmonary function studies in normal boys. *Arch. Dis. Childh.*, **32**, 347.
Stewart, C. A. (1922). The vital capacity of the lungs of children in health and disease. *Amer. J. Dis. Child.*, **24**, 451.
Strang, L. B. (1959). The ventilatory capacity of normal children. *Thorax*, **14**, 305.
Thomson, W. B. and Hugh-Jones, P. (1958). Forced expiratory volume as a test for successful treatment of asthma. *Brit. med. J.*, **1**, 1093.
Thursby-Pelham, D. C. and Kennedy, M. C. S. (1958). Prednisolone compared with cortisone in treatment of children with chronic asthma. *Brit. med. J.*, **1**, 243.
Tiffeneau, R., Bousser, J. and Drutel, P. (1949). Capacité vitale et capacité pulmonaire utilisable à l'effort: critères statiques et dynamiques de la ventilation pulmonaire. *Paris méd.*, **137**, 543.
Whitwell, F. (1952). A study of the pathology and pathogenesis of bronchiectasis. *Thorax*, **7**, 213.

MEASUREMENTS OF
PULMONARY DIFFUSING CAPACITY IN CHILDREN

BY

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Since the early studies of the Kroghs (Krogh, 1915) a number of investigators have employed low concentrations of carbon monoxide (CO) in order to study the diffusing capacity of the lungs. Carbon monoxide is taken up avidly by red blood cells in the pulmonary capillaries as it has 210 times the affinity for haemoglobin that oxygen has. For this reason, during the breathing of low concentrations of CO the tension of this gas in the blood plasma may be regarded as zero. If this assumption is made the diffusing capacity of the lungs for CO (Dco) can be derived from a knowledge of the mean alveolar CO concentration and the uptake of CO over a fixed time interval. Difficulties arise mainly in arriving at a valid figure for the mean alveolar CO tension and in controlling the variations in diffusing capacity which occur in differing states of rest or exercise. The diffusion velocities of carbon monoxide (CO) and oxygen (O_2) are proportional to the ratio of their solubilities and inversely proportional to the ratio of the square roots of their molecular weights. The diffusing capacities of the lung for CO and O_2 (Dco and Do_2) can be regarded as similarly related, the Dco being converted to Do_2 by multiplying by a factor of $1 \cdot 23$ (Krogh, 1915).

A number of clinical methods have been devised for measuring the Dco using either steady state or single breath methods (Filley, MacKintosh and Wright, 1954; Forster, Fowler, Bates and Van Lingen, 1954; Bates, Boucot and Dormer, 1955; Gilson and Hugh-Jones, 1955; Ogilvie, Forster, Blakemore and Morton, 1957). The values obtained in normals and in patients with pulmonary diseases differ depending on the method used, the greatest difference being between single breath and steady state procedures. Because of these discrepancies and for other reasons the exact significance of these methods and the differences between them is rather uncertain. Nevertheless, there is no doubt

that abnormalities affecting gas uptake in the lungs can be detected by one or other of them, and in approaching the general problem of pulmonary function testing in children it seemed reasonable to use a CO method in order to estimate the possible extent of gas exchange abnormalities in children with pulmonary disease.

It was preferred to use a method involving a minimum of discomfort for the child and no arterial punctures and for these reasons a method of Bates (Bates *et al.*, 1955) with some simplifications was employed.

In this method the CO tension of an end-tidal sample is taken as representing the mean alveolar tension of this gas.

Methods

Clinical Material. Four groups were examined: 79 normal children, 37 with bronchiectasis, 15 with asthma, and two with diffuse pulmonary disease.

The normal children were hospital in-patients and out-patients in whom cardiac and pulmonary disease had been excluded on clinical grounds. Thirty-five were girls, 44 were boys, and their ages were 5-14 years. Each child was tested on one occasion.

The 37 children with bronchiectasis were included in a previous study of ventilatory capacity abnormalities (Strang, 1960). All of them had cough, purulent sputum and abnormal segmental opacities on plain radiographs of the chest, and in 34 of them the presence of bronchiectasis had been confirmed on bronchography. Fifty-eight measurements of Dco were performed, 16 of the children being tested on two or more occasions. To allow comparison of functional and clinical data these patients were allocated to three grades of severity of symptoms and into three categories of increasing diffuseness of râles or rhonchi on auscultation of the chest. An exact definition of the groups is contained in a previous paper (Strang, 1960). The child was allocated to the categories without knowledge of the results for Dco. For comparison with radiological appearances a count was made of the numbers of bronchopulmonary segments seen to be involved on plain radiographs and bronchograms.

The 15 children with asthma were each tested on one

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occasion. Eosinophilia and impaired ventilatory capacity had been detected at some stage in each of them. None of them had permanent segmental shadows in plain radiographs of the chest but four of them habitually expectorated purulent sputum.

Of the two children with diffuse pulmonary disease one child had severe pulmonary infection associated with fibrocystic disease of the pancreas, and the other, idiopathic pulmonary haemosiderosis. The latter child had had repeated haemoptyses over a period of five years and radiological changes characteristic of the condition. Each of these children was tested on three separate occasions.

Apparatus and Procedure. The apparatus (Fig. 1) consisted of a 50 litre plastic bag A connected by a two-way tap and 0·75 in. diameter tubing to a 'Ruben' valve assembly B. This was fitted with a 'B.M.R.' mouthpiece and connected by tubing on the expiratory side to a 15 litre plastic bag C fitted with a two-way tap. The 'Ruben' valve was modified to include an Otis-Rahn end-tidal sampler D and this was connected by a sampling pump to a small 0·5 litre plastic bag E fitted with a two-way tap.

The bags were arranged on either side of a small table and the valve assembly and mouthpiece were attached to the table by an easily adjusted flexible clamp holder. During testing, the child sat comfortably at the table and, after a brief settling-down period, was connected to A which contained a prepared mixture of 0·1% CO in air. At the same time the Otis-Rahn sampler was connected to the pump operating at 250 ml. per min. After 1·5-2 min. to allow for clearing of the dead space of the apparatus and equilibration in the lungs, the expired gas was collected in C for 1 min. by a stopwatch. The end-tidal sample was collected over 1·5 min. which ensured an adequate size of sample. At the end of the procedure, the concentrations of CO in the inspired, expired and end-tidal samples were measured by passing through an infra-red gas analyser,* and the volume of gas in bag C was measured by passing it through a gas meter.† The minute ventilation was taken as this volume plus the volume removed for sampling and the volume of the end-tidal sample.

From these readings the Dco (in ml./min./mm. Hg partial pressure difference of CO) was calculated according to the following expression, the tension of CO in the pulmonary capillary blood being taken as zero:

$$Dco = \frac{\dot{V}(FI - FE)}{FET. \ (B - 47)}$$

(where $\dot{V}$ is minute ventilation, FI, FE and FET, are fractions of CO in inspired, expired and end-tidal gas, and B is barometric pressure).

Each child was tested twice and the result expressed as a mean of the two readings. The amount of blood inactivated by conversion of haemoglobin to carboxyhaemoglobin was estimated to be in the order of 30-50 ml. for the whole procedure.

Results

Normals. The coefficient of variation of a single estimate of Dco was 10·2%. A significant positive correlation was found between Dco and the child's height, weight, surface area and age (Table 1). The correlation with surface area was better than with the other parameters tested but that with height was almost as good and the results are presented as a regression on the height with intervals of two standard deviations (Fig. 2).

TABLE 1

CORRELATIONS OF Dco WITH AGE AND VARIOUS BODY MEASUREMENTS (79 NORMAL CHILDREN)

				Correlation Coefficient (r)
Surface area	..	..	..	0·654
Height	..	..	..	0·635
Weight	..	..	..	0·620
Age	..	..	..	0·511

Bronchiectasis. The results in 34 children with bronchiectasis are shown in Fig. 3 and compared with the normal limits for height. Relatively few of these results were outside the normal limits but there was a trend towards lower values. This was shown in a significant difference between the mean of this group and the normals when both sets of data were expressed as a percentage of the normal mean for height. (Normal mean—100%, S.E.=2·17, n=79; Bronchiectasis mean=79%, S.E. 2·87, n=58.)
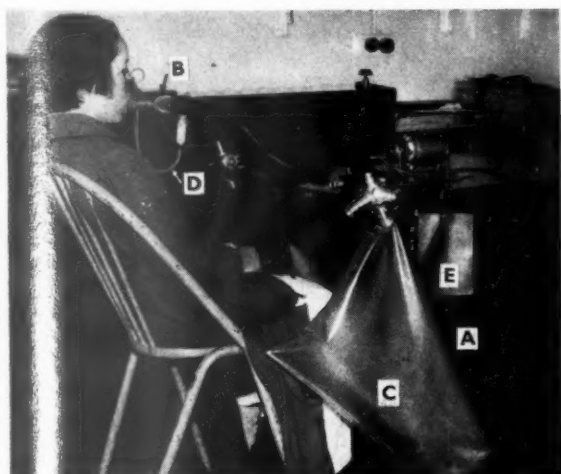
FIG. 1.—Apparatus for measurement of Dco—see text.
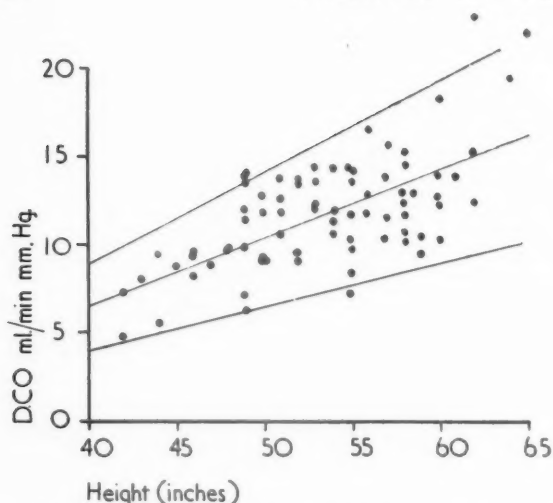
FIG. 2.—Dco of 79 normal children by height. 35 girls, 44 boys. Regression: Dco ml./min./mm. Hg=0·390 × Ht. (in.)−9·1. (Coefficient of variation between children=19·3%. 95% limits shown.
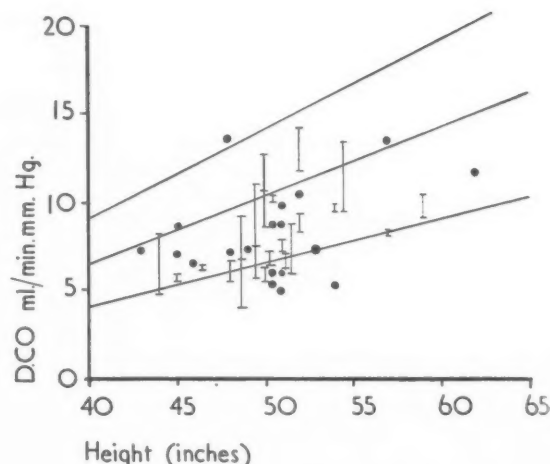
FIG. 3.—Dco of 37 children with bronchiectasis compared with normal limits for height. 58 observations. Repeated observations on one child are joined by a vertical line.

There appeared to be no significant relationship between Dco and the grades of severity or diffuseness of the bronchiectasis (Tables 2 and 3) and no obvious correlation with the numbers of abnormal segments counted on chest radiographs.

Asthma. The results are shown in Fig. 4 and compared with the normal limits for height. These patients were in differing states of ventilatory impairment, six of them having diffuse rhonchi on auscultation at the time of testing. The results,

however, showed no important difference from the normal and they were not analysed further.

Diffuse Pulmonary Lesions. The results on these two patients, each tested on three separate occasions, are shown in Fig. 5 and compared with the normal limits for height. The child with fibrocystic disease was within normal. The child with idiopathic pulmonary haemosiderosis had a severe impairment of diffusing capacity and this finding was highly repeatable.
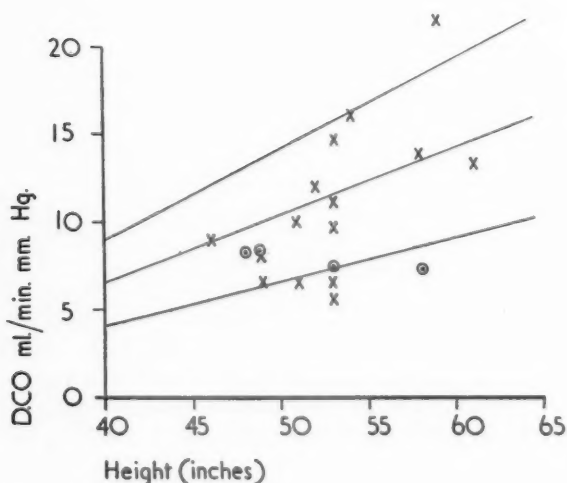
FIG. 4.—Dco of 15 children with asthma. Crosses represent children with no overt pulmonary infection. Circles represent children with purulent sputum.

o idiopathic pulmonary haemosiderosis
□ fibrocystic disease of pancreas
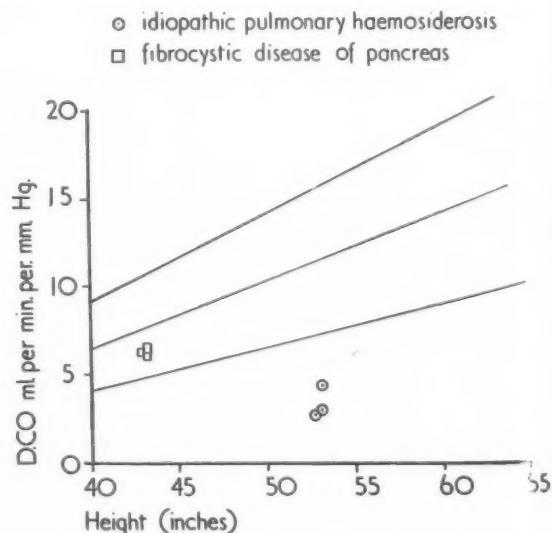
FIG. 5.—Dco in two children with diffuse pulmonary disease

TABLE 2

Dco AND CLINICAL ESTIMATE OF SEVERITY OF BRONCH-
IECTASIS (59 OBSERVATIONS, 34 CHILDREN)

Grade of Severity	No. of Observations	Mean Dco (% normal)	t	p
1	18	81·6	0·337	>0·05
2	31	79·4		
3	10	72·0	1·065	>0·05

TABLE 3

Dco AND DIFFUSENESS OF SIGNS ON AUSCULTATION
(59 OBSERVATIONS, 34 CHILDREN)

Grade of Diffuseness	No. of Observations	Mean Dco (% normal)	t	p
1	19	84·2	1·49	>0·05
2	19	75·1		
3	21	76·4		

Discussion

The Method. The method used to measure Dco can be criticized on at least two grounds. First, it could not be ensured that the children were completely at rest or in comparable states of activity during the procedure and some of them tended to hyperventilate. Second, it is quite possible that the end-tidal sample did not represent a true mean of the alveolar gas, the poorly ventilated areas of lung probably being under-represented. Alternative means of arriving at this value include calculation from the arterial CO_2 tension (Filley *et al.*, 1954), calculation from the Bohr equation using an assumed value for the anatomical dead-space (Bates *et al.*, 1955) or the use of a single breath method after preliminary estimation of the functional residual capacity (Ogilvie *et al.*, 1957). The first of these was not used because arterial punctures were considered undesirable in these patients; the second could not be used because reliable data for anatomical dead-space are lacking in children. The third possibility was rejected because it was thought that the timing of breath holding would require too great a degree of cooperation.

Normal Values. The results in normal children are presented as a regression on the standing height because this appears to be a better basis for comparison between normals and children with pulmonary disease than the weight or surface area which is derived from the height and weight. This is because children with pulmonary disease are frequently below normal in weight but seldom in height (Strang, 1960). The height was used as a basis for comparison in previous studies of ventilatory capacity and this is an additional reason for using it here, particularly as the correlation is only slightly less good than that with surface area.

Results in Pulmonary Diseases. Significant abnormalities of diffusing capacity would appear to be rare in children. The only undoubted example detected in this study was in the child with idiopathic pulmonary haemosiderosis. This finding was highly repeatable and it is probable that other similar defects could be detected by this method. Diffuse infiltrative lesions of the lungs such as this are rare in childhood and the measurement of diffusing capacity is likely, therefore, to have a very limited application. It is certainly unlikely to be useful in studies of asthma and bronchiectasis.

The overall Dco measured by any steady-state technique such as the present one is dependent on the balance between ventilation and blood flow, and when inequalities of ventilation–bloodflow ratios exist, they will lead to lower values for the overall diffusing capacity, without there necessarily being any obstacle to diffusion in any individual part of the lung (Forster *et al.*, 1954). Bronchiectasis in children is a diffuse patchy condition (Whitwell, 1952) which might be expected to be associated with inequalities of ventilation and bloodflow, and it may be that the lower than normal values of Dco obtained in these children are due to this rather than to an impairment of diffusing capacity as usually understood. If this is so, an investigation of ventilation–bloodflow inequalities in this group might be rewarding.

Summary

Measurements of the diffusing capacity for carbon monoxide (Dco) in children are presented. The method appears to have a limited application in the study of pulmonary diseases in children.

REFERENCES

Bates, D. V., Boucot, N. G. and Dormer, A. E. (1955). The pulmonary diffusing capacity in normal subjects. *J. Physiol.* (*Lond.*), 129, 237.
Filley, G. F., MacKintosh, D. J. and Wright, G. W. (1954). Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *J. clin. Invest.*, 33, 530.
Forster, R. E., Fowler, W. S., Bates, D. V. and Van Lingen, B. (1954). The absorption of carbon monoxide by the lungs during breath-holding. *J. clin. Invest.*, 33, 1135.
Gilson, J. C. and Hugh-Jones, P. (1955). Lung function in coal-workers' pneumoconiosis. *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 290.
Krogh, M. (1915). The diffusion of gases through the lungs of man. *J. Physiol.* (*Lond.*), 49, 271.
Ogilvie, C. M., Forster, R. E., Blakemore, W. S. and Morton, J. W. (1957). A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J. clin. Invest.*, 36, 1.
Strang, L. B. (1960). Abnormalities of ventilatory capacity in children with asthma and bronchiectasis. *Arch. Dis. Childh.*, 35, 224.
Whitwell, F. (1952). A study of the pathology and pathogenesis of bronchiectasis. *Thorax*, 7, 213.

NORMAL STANDARDS FOR SINGLE BREATH TESTS OF VENTILATORY CAPACITY IN CHILDREN

BY

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Tests of ventilatory capacity based on the recording of a maximum forced expiration after a full inspiration are becoming increasingly widely used. They are quicker to perform and require less cooperation and effort on the part of the subject than the conventional maximum breathing capacity estimation, and the results are more informative because three indices of ventilatory capacity, each of different significance, are derived from the recording of this simple manoeuvre. These indices are: (1) the forced vital capacity, (2) the volume of gas expired over a given time interval (usually the first second or half second), and (3) the percentage of the vital capacity (or forced vital capacity) expired within the same time period (that is, 2 as a percentage of 1). In this department the procedure has been found most appropriate in paediatric work; the children learn it readily and can repeat it frequently with, in my experience, greater consistency than the maximum breathing capacity test.

Adequate normal standards are available for the vital capacity (Turner and McLean, 1951; Jones, 1955), and this paper provides data relating to the percentage of the vital capacity expired in the first second and half second of a forced expiration.

Definitions and Terminology

The recording obtained when the subject, after a full inspiration, forcibly and completely exhales into a spirometer, the movement of which is recorded with a kymograph, is termed the forced expiratory spirogram (F.E.S.). The volumes of gas exhaled in the first half second and the first second of expiration are termed the forced expiratory volume at half a second (F.E.V.$_{0.5}$) and one second (F.E.V.$_{1.0}$) respectively. The total volume of gas expired is termed the forced vital capacity (F.V.C.). The qualification 'forced' is added to distinguish this measurement from the vital capacity (V.C.) estimated in the conventional manner, that is, when the expiration, in the earlier phases at least, is comparatively 'unforced'. The distinction is necessary because in certain pathological states the values for the vital capacity differ according to whether the expiration is forced or not; in emphysema, for example, 'air-trapping' leads to a forced vital capacity which is smaller than the vital capacity. The 'expired percentage' at 0.5 second or 1.0 second is the percentage of the V.C.* expired in the appropirate time interval and is abbreviated to F.E.V.$_{0.5}$% or FEV$_{1.0}$%; it is therefore equal to $\dfrac{\text{F.E.V. } 0.5}{\text{V.C.}} \times 100$ or $\dfrac{\text{F.E.V. } 1.0}{\text{V.C.}} \times 100$.

The terminology set out above is in accord with that adopted and recommended for general usage by the Thoracic Society of Great Britain (Gandevia and Hugh-Jones, 1957). It replaces or modifies a remarkable variety of different names employed by different workers in different countries for tests and their results which are essentially similar.

Methods

The spirometer used was of the type described by Bernstein and others (1952) to minimize various errors in the response of the bell to the sudden entry of gas. All connexions were of wide bore to reduce resistance to gas flow. The patient fitted a valveless anaesthetic mask, of adult or child size, with a one-inch outlet, to his face; a face mask has been found more convenient and less disturbing for the patient than the usual mouthpiece and noseclip. A Palmer kymograph was set to give a paper speed of 3.0 cm. per second. No timing device was employed during the recordings but the speed of the kymograph was periodically checked against a mechanical time-marker. Tracings were not begun until the drum had moved approximately 10 cm. One

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* The F.V.C. is used by many workers in preference to the V.C. However, the latter is the more repeatable estimation and, in my view, the more fundamental characteristic. Numerically the difference is negligible except when there is significant 'air-trapping'.

centimetre of travel of the bell was produced by the entry of 300 ml. of gas; this calibration was carefully checked by direct measurement of the internal diameters of the bell throughout its length.

After their height* (without shoes) had been measured the subjects were seated at a comfortable height in relation to the spirometer. The tests were explained and the fit of the face mask demonstrated and checked. The V.C. was then estimated in the conventional manner. Several recordings of forced expiration were made. The number of recordings of vital capacity and of forced expiration varied from subject to subject; four 'satisfactory' recordings of vital capacity and three of forced expiration were required, the mean value of these estimates being accepted. By 'satisfactory' is meant a recording free of artefacts and of mistakes on the part of the subject as judged by eye. Misleading tracings due to misunderstanding or obviously incomplete co-operation were discarded. In most instances 'satisfactory' therefore implies reasonable consistency. The statistical criticisms of this procedure are appreciated but it was used because it must necessarily be the approach adopted in clinical practice. From two subjects ($1 \cdot 3\%$) it was found impossible to obtain satisfactory recordings. It was usual for the subject to have watched two or three of his colleagues do the tests before his turn came.

The values for F.E.V.$_{0 \cdot 5}$, F.E.V.$_{1 \cdot 0}$ and the V.C. were derived from these tracings and F.E.V.$_{0 \cdot 5}\%$ and F.E.V.$_{1 \cdot 0}\%$, with which this paper is primarily concerned, were calculated.

Children Studied. The children studied attended four government schools, two in an industrial area and two in residential suburbs. As the findings were similar in the two areas the results were pooled. A total of 91 males and 79 females between the ages of 5 and 14 years were examined; the numbers at each year of age are set out in Table 1. Care was taken to avoid selection on any obvious grounds, such as intelligence or physical prowess,

and volunteers were not called. The study was conducted in conjunction with the periodical examinations conducted by school medical officers. Children with asthma, chronic pulmonary infection, moderate or severe thoracic deformity and very occasional subjects with extremely poor posture and physique were excluded. Approximately 10% of the children were immigrants; their results were comparable with those of Australian children.

TABLE 1
AGE DISTRIBUTION OF SUBJECTS

Year of Life	Number of Patients	
	Female	Male
6	3	3
7	7	4
8	1	7
9	10—21	7—21
10	7	11
11	9	10
12	12	10
13	14	25
14	16—58	14—70
Total	79	91

Results

The correlation coefficients and regression equations relating F.E.V.$_{0 \cdot 5}\%$ and F.E.V.$_{1 \cdot 0}\%$ to age and standing height are set out in Table 2 for both the male and female series. In the latter there is a good correlation between F.E.V.$_{0 \cdot 5}\%$ and F.E.V.$_{1 \cdot 0}\%$ and each of the other parameters; all the correlation coefficients are significant at the 1% level. In the male series significant correlations are found only in relation to F.E.V.$_{0 \cdot 5}\%$, while those for F.E.V.$_{1 \cdot 0}\%$ are virtually zero. The reason for this lies in the stability of F.E.V.$_{0 \cdot 5}\%$ and F.E.V.$_{1 \cdot 0}\%$ over the whole range of age or height in the boys, whereas in the

TABLE 2
CORRELATION COEFFICIENTS AND REGRESSION EQUATIONS FOR F.E.V. $_{0 \cdot 5}\%$ AND F.E.V. $_{1 \cdot 0}\%$ ON STANDING HEIGHT AND AGE

Procedure	Sex	r	Regression Equation	95% Tolerance Limits at Mean Values
F.E.V.$_{0 \cdot 5}\%$ on standing height (S) (in.)	F	$0 \cdot 577$**	F.E.V.$_{0 \cdot 5}\% = 115 \cdot 2 - 0 \cdot 993$ S	$\pm 16 \cdot 6$
	M	$0 \cdot 216$*	F.E.V.$_{0 \cdot 5}\% = 81 \cdot 7 - 0 \cdot 403$ S	$\pm 20 \cdot 8$
F.E.V.$_{0 \cdot 5}\%$ on age (A) (mth.)	F	$0 \cdot 547$**	F.E.V.$_{0 \cdot 5}\% = 85 \cdot 0 - 0 \cdot 193$ A	$\pm 17 \cdot 0$
	M	$0 \cdot 273$**	F.E.V.$_{0 \cdot 5}\% = 72 \cdot 7 - 0 \cdot 105$ A	$\pm 20 \cdot 5$
F.E.V.$_{1 \cdot 0}\%$ on standing height (S) (in.)	F	$0 \cdot 372$**	F.E.V.$_{1 \cdot 0}\% = 113 \cdot 9 - 0 \cdot 561$ S	$\pm 16 \cdot 5$
	M	$0 \cdot 063$	F.E.V.$_{1 \cdot 0}\% = 87 \cdot 1 - 0 \cdot 098$ S	$\pm 17 \cdot 8$
F.E.V.$_{1 \cdot 0}\%$ on age (A) (yr.)	F	$0 \cdot 336$**	F.E.V.$_{1 \cdot 0}\% = 96 \cdot 2 - 0 \cdot 104$ A	$\pm 16 \cdot 8$
	M	$0 \cdot 053$	F.E.V.$_{1 \cdot 0}\% = 83 \cdot 9 - 0 \cdot 017$ A	$\pm 17 \cdot 8$

Degrees of freedom: females, 77; males, 89; * significant at 5% level; ** significant at 1% level.

* Stem height was also measured but subsequent statistical analysis indicated that it offered no advantage over the simpler measurement of standing height in the prediction of any of the ventilatory indices. The results obtained in relation to stem height were similar in all respects to those for standing height.

girls there is a pronounced fall in both values. Fig. 1a shows the regression lines for the absolute values of F.E.V.$_{0 \cdot 5}$, F.E.V.$_{1 \cdot 0}$ and V.C. on standing height for both sexes. The increase in V.C. with increasing
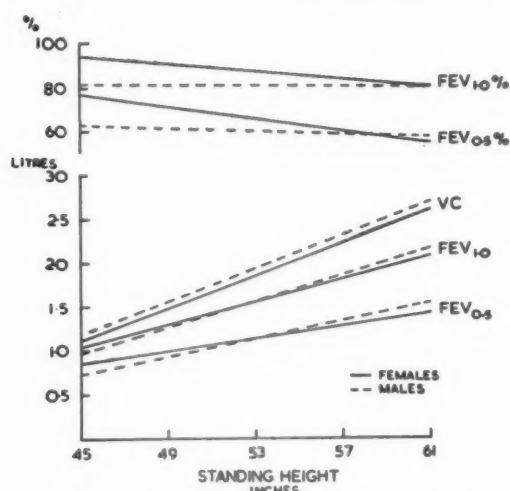
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FIG. 1(a).—(lower graph)—Regression lines for absolute values of F.E.V. $_{0.5}$ F.E.V. $_{1.0}$ and V.C. on standing height for both sexes.
FIG. 1 (b).—(upper graph)—Relates values for F.E.V. $_{0.5}\%$ and F.E.V. $_{1.0}\%$ (calculated from regression lines in Fig. 1(a)) to standing height for both sexes.

height is similar in girls (continuous lines) and boys (broken lines), but in the boys F.E.V.$_{0.5}$ and F.E.V.$_{1.0}$ increase more with increasing height and more in relation to the V.C. than is the case with the girls. This is reflected in the graph (Fig. 1b) relating values for F.E.V.$_{0.5}\%$ and F.E.V.$_{1.0}\%$, as calculated from the regression lines in Fig. 1a, with standing height; the calculated values may be compared with the regression lines for the actual values (Figs. 2 and 3). Separate analysis of the results for children of 9 years of age and above and for children less than 9 years old revealed the same pattern of results in all groups as in the two series as a whole. There was therefore no evidence to suggest that lack of

cooperation on the part of the older girls or younger boys would serve as an explanation of the relative 'expiratory inefficiency' of those groups. Grouping by age according to the mean values for the ventilatory indices or according to the totals does not affect the findings set out above.

Results of multiple regression analysis showed that little was gained in the prediction of normal values by employing the regression line of F.E.V.$_{0.5}\%$ or F.E.V.$_{1.0}\%$ on both standing height and age. The influence of age is small relative to that of height and its inclusion does not materially reduce the tolerance limits. It may be added that further analysis of the absolute values of F.E.V.$_{0.5}$, F.E.V.$_{1.0}$ and V.C. in relation to standing height and age showed a similarly negligible effect of age.

Discussion

The results obtained for vital capacity in this survey are almost identical with those of other observers and hence the present paper is confined chiefly to a consideration of the values for the percentage of the vital capacity expired in the first half-second and first second of a forced expiration. In clinical work, prediction of normal values based on age alone is obviously unsatisfactory because it ignores the important factor of size. In the present study, as in others, age (over the range studied) was found to exert little effect on the several indices of ventilatory capacity compared with the effect of size as indicated by standing or stem height. Standing height is a simple and routine measurement in most paediatric clinics and, as stem height was found to offer no significant advantage, it forms an appropriate basis for the prediction of normal values.

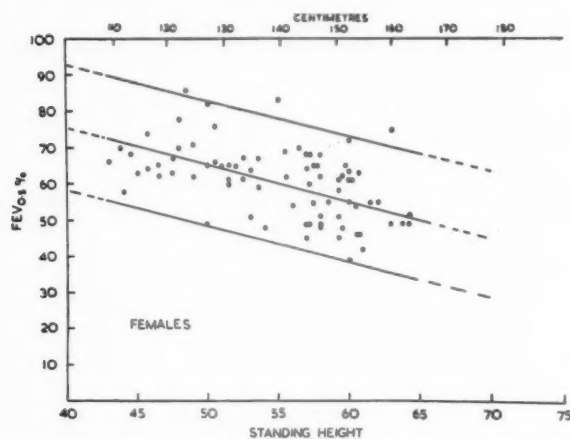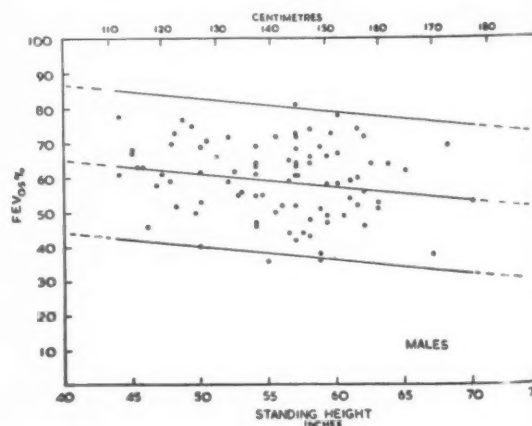In females F.E.V.$_{0.5}\%$ ranged from 70% at a

FIG. 2a.   FIG. 2b.

FIG. 2.—Actual values for F.E.V.$_{0.5}\%$ plotted against standing height with regression lines and 95% tolerance limits: (a) females, (b) males.
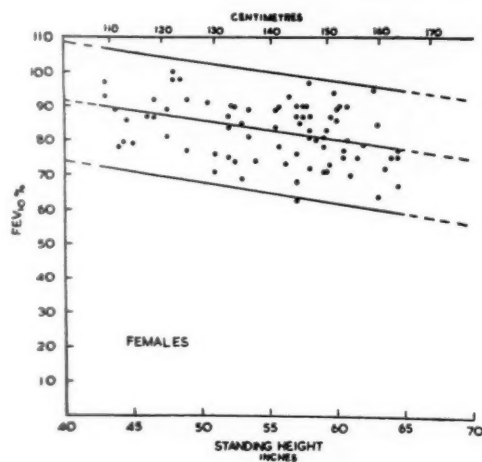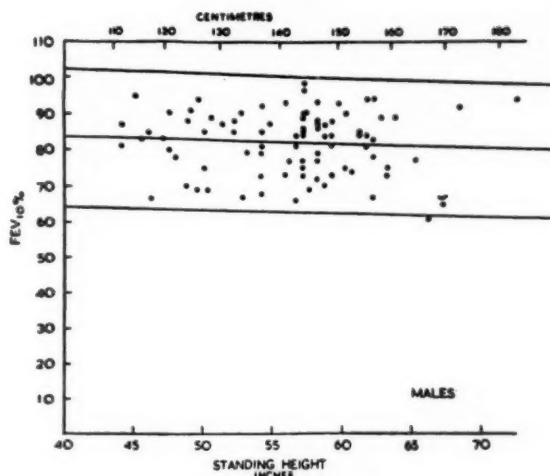
FIG. 3a.

FIG. 3b.

FIG. 3.—Actual values for F.E.V. $_{1.0}$% plotted against standing height with regression lines and 95% tolerance limits: (*a*) females, (*b*) males.

height of 45 in. (114 cm.) to 50% at 65 in. (165 cm.) and F.E.V.$_{1.0}$% from 88% to 77% with 95% tolerance limits of $\pm$17% in each case. In the males F.E.V.$_{0.5}$% ranged from 63% at 45 in. (114 cm.) to 55% at 65 in. (165 cm.) and F.E.V.$_{1.0}$% from 82% to 78% with 95% tolerance limits of $\pm$20%. As the increase of vital capacity with increasing height is similar in boys and girls the difference in behaviour is due to different 'rates' of increase in F.E.V.$_{1.0}$ and F.E.V.$_{0.5}$ with increasing height; in young boys the absolute values for these indices are lower than for girls (although the V.C. is higher) but over a height of about 4 ft. 6 in. the boys have the higher values (although the V.C. increase in boys and girls is the same). No explanation for this sex difference is apparent but it is worth noting (*a*) that the similarity of the line relating V.C. and height in boys and girls has been reported in other studies, and (*b*) that at the age of 14 years the present values for F.E.V.$_{0.5}$% and F.E.V.$_{1.0}$% are those regarded as normal for adults of both sexes. These observations, combined with the finding that the results are similar when the younger and older children are studied as separate groups, suggest that the difference between the sexes is a real one and is

not attributable to lack of cooperation on the part of any sub-groups in the performance of the vital capacity or forced expiration manoeuvres.

Summary

Indices of ventilatory capacity derived from the forced expiratory spirograms of a series of healthy school children are related to standing height.

Attention is drawn to certain differences between the sexes in regard to the proportion of the vital capacity expired in the first second or half-second of a forced expiration.

REFERENCES

Gandevia, B. and Hugh-Jones, P. (1957). Terminology for measurements of ventilatory capacity: A report to the Thoracic Society. *Thorax*, 12, 290.
Jones, H. E. (1955). The vital capacity of children. *Arch. Dis. Childh.*, 30, 445.
Turner, J. A. and McLean, R. L. (1951). Spirometric measurements of lung function in healthy children. *Pediatrics*, 7, 360.

THE CEREBRO-OCULAR-RENAL DYSTROPHIES: A NEW VARIANT

BY

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Under this title it is proposed to describe a syndrome which has been under observation in two brothers, both of whom have now died. The syndrome is characterized clinically by anorexia, failure to grow, muscular hypotonia, corneal opacities and mental retardation; and physiologically by a severe hyperchloraemic acidosis, a very acid urine and a noteworthy defect on the part of the kidney to excrete ammonium ions. Progressive renal deterioration has been the cause of death. The disease thus belongs in a way to that ill-defined group described by Lowe, Terry and MacLachlan (1952), Royer and Prader (1957), Debré, Royer, Lestradet and Straub (1955) and also perhaps Goldbloom, Fraser, Waugh, Aronovitch and Wiglesworth (1957). It differs from all of them, however, in the nature of the renal lesion. It has been possible to make clinical, biochemical and post mortem investigations which will each to some extent be considered separately.

Clinical Histories and Biochemical Findings

The Family. The two patients were brothers, the only children of normal and unrelated English parents. A female sibling was stillborn. Their father has two healthy brothers; their mother a clinically normal sister. Forty other members of the family have been traced without finding any evidence or records of the syndrome.

Case 1 (M), a male child, was born on May 5, 1954. Pregnancy and delivery were normal. His weight at birth was $2 \cdot 4$ kg. and the circumference of his skull $32 \cdot 5$ cm. He was breast fed for three months, but from the start took his food badly, and showed an increasing tendency to vomit from the age of 3 months. He was brought to the hospital at Leicester on account of his eyes and there he was found to have corneal opacities, nystagmus and intense photophobia. He failed to reach the normal milestones and was considered very 'backward' and mentally retarded by the age of 6 months. He was, therefore, sent to a London hospital in Decem-

ber, 1955, where the diagnosis of blindness, corneal opacities and mental retardation was confirmed. Pneumo-encephalograms, however, disclosed no abnormality. His cerebrospinal fluid (C.S.F.), obtained 20 to 40 min. after the encephalogram was started, contained 110 mg. of protein/100 ml. and 40 cells/c.mm. His renal function was not investigated.

In November, 1956, he was admitted to Leicester Infirmary under W.J.M. for further investigation. By this time he had had one or two major convulsions. He had a little less photophobia but otherwise his mental and ocular abnormalities seemed unchanged. His reflexes were all active and normal. His systolic blood pressure was found to be 145 mm. Hg by the flush method, but a narrow cuff was used and this figure may have been too high. Blood was withdrawn for examination and the most striking finding was the low concentration of 'total CO_2'. Other results were—serum calcium 10 mg./100 ml. and alkaline phosphatase $12 \cdot 4$ King Armstrong units. The findings in the serum and urine a few months later are summarized in Tables 1 and 2 and will be discussed after the clinical histories. The child's renal tract was visualized satisfactorily by intravenous pyelography and appeared to be normal. His urine was consistently very acid and specific gravities of 1017-1018 were reached in concentration tests. Paper chromatography (Dr. H. Bickel) disclosed no abnormal amino-acids and this finding was confirmed a year later in another laboratory (Professor C. E. Dent). This excluded phenyl ketonuria and the amino-acid pattern of his serum, which was also investigated by Professor C. E. Dent, was found to be normal as well. No evidence of cystinosis has been found by any of the tests applied.

He was admitted to Addenbrooke's Hospital, Cambridge, on January 11, 1957, aged $2\frac{1}{2}$ years. By this time he had had further convulsions. He weighed $8 \cdot 4$ kg. (normal for age $16 \cdot 0$ kg.); his height was 75 cm. (normal 95 cm.), and his skull and chest measurements were both 44 cm. (normal 50 cm.). His fontanelle had closed. He had nystagmus, and an examination of his eyes under general anaesthesia revealed corneal opacities, but no abnormality in his lenses or fundi, and it was considered that he could distinguish light and shade, and probably also recognize shapes. He had some

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TABLE 1

THE CONCENTRATION OF ELECTROLYTES AND OF CERTAIN OTHER SUBSTANCES IN THE SERUM OF THE PARENTS, THE MOTHER'S SISTER AND THE TWO CHILDREN

	Na (mEq./l.)	K (mEq./l.)	Cl (mEq./l.)	Total CO_2 (mEq./l.)	Inorganic P (mg./100 ml.)	Creatinine (mg./100 ml.)	Urea (mg./100 ml.)	Protein (g./100 ml.)
Normal values (various sources)	130–150	4·1–5·6	98–106	22·5–32·9*	2–5 a 4–6 c	0·7–2·0	15–40	6·5–8·2
Father	139	4·4	102	28·4	—	1·2	30	—
Mother	140	4·3	105	25·7	3·6	0·9	24	—
Maternal aunt	150	4·1	107	23·4	—	1·6	24	—
Older child (M)	132	6·5	109	13·7	4·9	1·5	112	7·7
Younger child (C)	130	7·6	110	11·7	8·4	—	100	6·1

* Unpublished data from J. R. Elkinton's laboratory based on 142 determinations in 50 subjects.
a = adults.
c = children.

TABLE 2

ACID-BASE RELATIONSHIPS IN THE URINE OF NORMAL ADULTS AND BABIES, THE PARENTS, THE MOTHER'S SISTER, THE TWO PATIENTS, AND ADULTS AND CHILDREN WITH TYPICAL RENAL ACIDOSIS

	On normal diet					After 5 days ammonium chloride				
	pH	Titratable acidity (TA) (mEq./24hr.)	Ammonia (mEq./24hr.)	$\frac{NH_3 \times 100}{TA+NH_3}$	Inorganic P (mg./24hr.)	pH	Titratable acidity (TA) (mEq./24hr.)	Ammonia (mEq./24hr.)	$\frac{NH_3 \times 100}{TA+NH_3}$	Inorganic P (mg./24hr.)
Mean of 7 normal adults	5·9	26·0	23·0	47·0	799	4·6	47·0	84·0	66	984
Range				39–56					58–74	
Father	5·5	30·0	33·4	52·9	1,140	5·0	63·0	154·0	71	1,680
Mother	5·8	26·3	35·0	57·0	790	5·0	57·0	180·0	76	1,250
Maternal aunt	5·8	31·0	24·0	43·5	—	4·7	42·0	85·0	67	—
Normal babies (age 10 months)	6·3	4·8	5·9	55·0	141					
Older child (M)	4·9	7·4	2·9	28·0	228	5·4	7·0	12·4	64	142
Renal acidosis										
Adults (mean of 3)	6·4	12·1	23·2	66·7		5·8	27·2	47·8	65	
Children (mean of 6) (Latner and Burnard, 1950)	6·5	2·2*	5·2*	70·0	10†					

* m. mols./2 hr.　　　† mg./2 hr.

intention tremor and a flexor plantar response. He was unable to sit up unsupported, and his mental achievements were those of a child of 6 mths. His blood pressure by auscultation was found to be 95/60. His blood count was quite normal and remained so for the next year. He was examined radiologically with great care by Dr. F. R. Berridge, but nothing characteristic or diagnostic was found.

M. was treated for some time with enough sodium and potassium citrates to raise the total CO_2 in his plasma to about 23 mEq./l. At this level of plasma CO_2 he sometimes passed an alkaline urine (Schwartz, Hall, Hays and Relman, 1959), but his blood urea remained raised to between 80-100 mg./100 ml., and clinically he did not materially improve. He was discharged on March 7, 1957, readmitted April 5—June 27, again for a few weeks in August-September, and finally in late January, 1958. His weight was then 9·1 kg. and his height 86 cm. His physical signs were unchanged, but he had had more vomiting with some diarrhoea and had had more fits. His blood pressure was 120/90 and his blood urea on February 21 was 124 mg./100 ml. Gastric juice was removed and found to contain 15 ml. N HCl/100 ml. A lumbar puncture was performed

and normal fluid under normal pressure was removed. The amino-acid pattern of this fluid was examined by Professor C. E. Dent and no abnormalities were found. The concentration of glutamine was 7·8 mg./100 ml. Dr. J. M. Walshe, who kindly made this determination, considered the figure to be a normal one, as also was the one found for his blood ammonia.

An electro-encephalogram was recorded on February 4. It was reported upon as being very abnormal. No part of the cerebrum appeared to be functioning physiologically, and a lumbar puncture six days before could not be held responsible.

It was considered justifiable at this time to study M.'s reaction to acetazolamide. This was done while he was being treated with citrates and his plasma CO_2 was normal. Table 3 shows the results that were obtained after he had been given 188 mg. of acetazolamide/day. His urine became alkaline and the total CO_2 in his plasma fell from 30 to 16 mEq./l. The concentration of sodium in his serum fell at the same time from 138 to 127 mEq./l. It was concluded that this was the reaction of a person with a normal carbonic anhydrase mechanism in the renal tubules.

The boy was treated with 25 mg. of methyl testosterone

per day from February 14 to March 12. He improved clinically, gained some weight and became more alert, but his blood urea was 166 mg./100 ml. on the last date, and his treatment was then changed to 0·5 mg. of 9-α-fluorohydrocortisone. Three days later (March 15) he was obviously not so well, had become lethargic and had lost any inclination for food. The concentration of urea in his plasma was found to be 195 mg./100 ml. Next day his temperature had risen to 102° C., pulse to 160 and respirations to 60/min. His blood urea on March 17 was 263 mg./100 ml. and his haemoglobin was found to have fallen to 7·5 g./100 ml. He was accordingly given a transfusion of 250 ml. of whole blood followed by 100 ml. of $\frac{M}{6}$ sodium lactate since his plasma 'total CO_2' was only 13 mEq./l. He passed about 500 ml. of urine on March 15 with a specific gravity of 1008. His serum chemistry on March 19 was as follows: urea 277 mg./100 ml., Na 142, K 4·6, Cl 80 mEq./l., total CO_2 36·5 mEq./l. By this date he was passing very little urine and he died on March 23, 1958.

TABLE 3

THE EFFECT OF ACETAZOLAMIDE ON THE SERUM AND URINE OF THE ELDER SIBLING (M)

	Before Acetazolamide	After Acetazolamide
Urine pH	6·4	7·8
Serum Na mEq./l. ..	138	127
K ,, ..	6·1	6·8
Cl ,, ..	100	99
CO_2 ,, ..	30	16
Urea mg./100 ml. ..	153	209

Case 2 (C), the younger brother of M. was born on March 1, 1956. He weighed 3·1 kg. at birth and the circumference of his skull was 35 cm. He always took his food badly, and by 7 weeks had gained no weight. In the light of his elder brother's records he was suspected at this age of being mentally defective. After a few months he began to have attacks of vomiting. At the age of 7 months he was admitted to the Leicester Royal Infirmary. He weighed at this age 6·5 kg. He was 'floppy' and hypotonic and could not hold his head up, but his reflexes were normal. He did not appear to be blind but had corneal opacities, and did not follow a light with his eyes. His systolic blood pressure by the flush method was 70 mm. Hg; retinal vessels which could be seen were stated to be somewhat attenuated.

Samples of his blood were taken and analysed in November, 1956, and some of the results will be considered later (Table 1). Other findings in the serum at that time were calcium 9·6 mg./100 ml., and phosphatase 25·5 King Armstrong units. Samples of his urine were investigated by paper chromatography by Dr. H. Bickel on two occasions for unusual amino acids, but none were found. Several concentration tests were made and the highest specific gravity was 1017. The pH was consistently low and the lowest figure recorded was 5·0. An intravenous pyelogram was carried out, and both kidneys appeared to excrete the opaque material norm-ally. X-ray photographs showed no signs of osteo porosis or renal calcification.

The child contracted an intercurrent infection with diarrhoea in December, 1956, but death was probably the result of functional renal failure, for his blood urea, shortly before death, was found to have risen to 186 mg./ 100 ml. on December 26, 1956, and the pulmonary oedema found after death was considered to be uraemic in origin.

Acid-base Records and Comparisons

Table 1 shows the findings to be expected in a normal serum, and the results which were obtained on investigating the father and mother of the two children, the mother's sister, and the two children themselves. The figures given for M are the means of several samples all taken during his first two admissions to Addenbrooke's Hospital. It will be noted that no abnormalities were found in the father, mother, or mother's sister and that both children had low concentrations of sodium in their serum, high concentrations of potassium, and very low 'total CO_2'. They also had concentrations of urea above the normal limits, but the plasma levels of inorganic phosphorus and creatinine in M were essentially normal.

Table 2 shows the averaged findings for the 24 hour urines of six normal adults before and after the administration of 2 to 2·5 mEq. of ammonium chloride per kg. per day for five days. It also shows the results for the same test on the father and mother of the two children, and on the mother's sister. Results for some normal babies and some cases of juvenile renal acidosis are included; some of these have been taken from the literature. The results for M are given in heavy type. Unfortunately those for the young child, C, are limited. It will be seen that:

(1) The average pH for the seven normal persons on their customary diet was 5·9, and the percentage of the surplus anions excreted as ammonia, i.e. the ammonia × 100/ammonia+titratable acidity was 47. This conforms with the findings of Marriott and Howland (1918), Van Slyke, Linder, Hiller, Leiter and McIntosh (1926) and of Linder (1927). In this paper the equivalent of the titratable acidity+ammonia will be referred to as the 'surplus non volatile anions', or simply 'surplus anions'; in the absence of urinary bicarbonate this is a measure of the excretion of acid or hydrogen ions.

(2) After five days on ammonium chloride the pH of the normal urines had fallen to 4·6, the titratable acidity had increased, but to a smaller extent than the ammonia, and the percentage of the surplus anions excreted as ammonium salts had risen to 64; this was in accordance with expectation (Davies and Yudkin, 1952; Rector, Seldin and Copenhaver, 1955; Ryberg, 1948).

(3) No abnormalities were detected in the father or mother.

(4) The percentage of the surplus anions excreted by the mother's sister as ammonium salts on her customary diet may have been somewhat below the normal average, but it was not below the normal range and the response to an acid load was perfectly normal.

(5) The patients with renal acidosis were unable to achieve the normal acidification of the urine but the percentage of the surplus anions excreted as ammonium salts was quite normal.

(6) Both children were able to lower the pH of their urine to the normal extent, but the percentage of the surplus anions excreted by M as ammonium salts was abnormally low. It was, moreover, consistently so. Only one figure above 30 was obtained.

Post Mortem Findings

Naked Eye Appearances. A post mortem examination was conducted in both children, but in greater detail on the older child and the account which follows is based upon findings in the latter except where the younger child (C) is specifically mentioned.

There was nothing characteristic about the external appearances of either child. No abnormality was detected in the liver, gall bladder, bile ducts, spleen, portal vein or its branches. The same applies to the oesophagus, stomach, small and large intestine. The pancreas was of normal size in M's case but rather hard and the cut surfaces were very firm; the ducts were normal. All parts of the heart were normal; there was a normal distribution of the great vessels and their branches and the renal vessels were normal. The lungs of M showed tiny areas of collapse along the posterior borders but otherwise appeared normal; the air passages were lined by dry grey mucosa; the larynx, tonsils and middle ears were normal. As already mentioned the lungs of the young child (C) were oedematous. The bones were macroscopically normal; the costo-chondral junctions, the right femur and an entire vertebral strip were inspected. The pituitary, thyroid, thymus and suprarenal glands were all normal.

The brain was highly abnormal. Small sunken areas of atrophy were present in gyri of the superior parts of the parietal lobes (Fig. 1). There was also conspicuous cerebellar atrophy. The cerebellum as a whole was
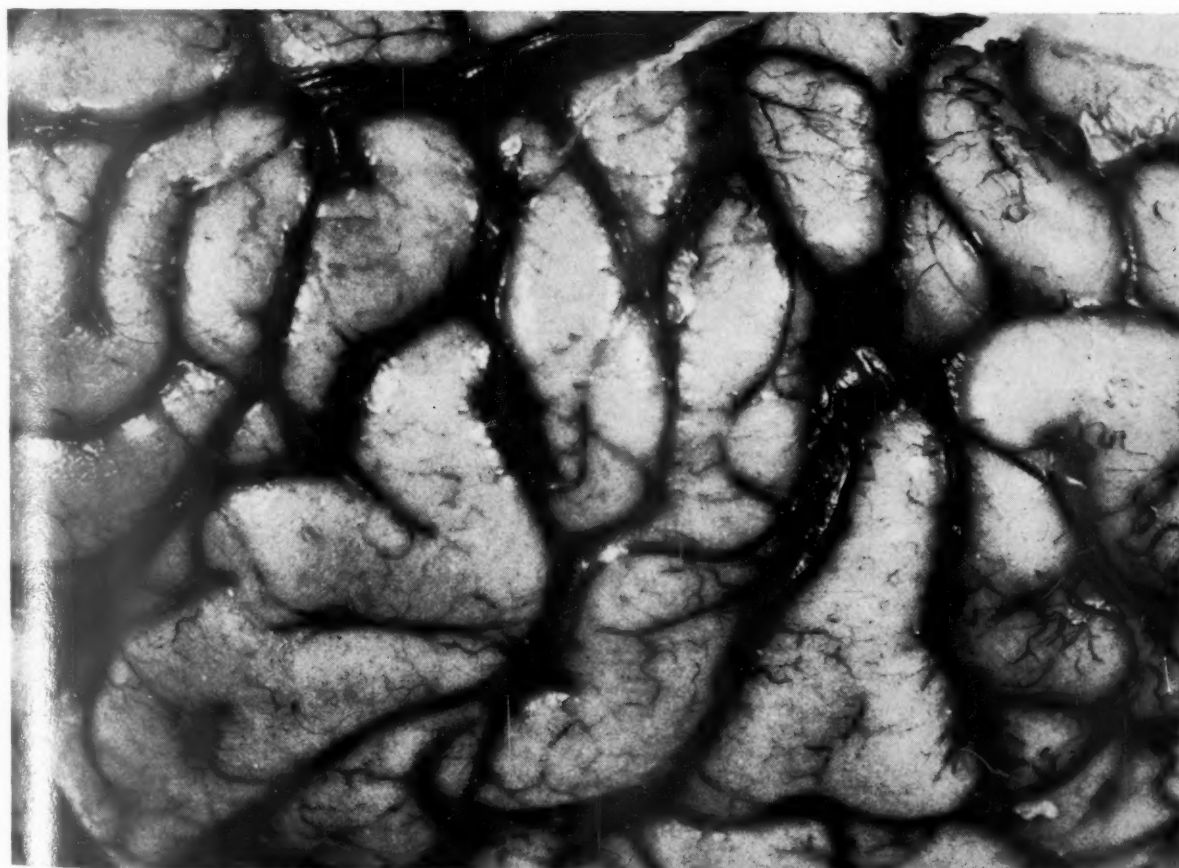

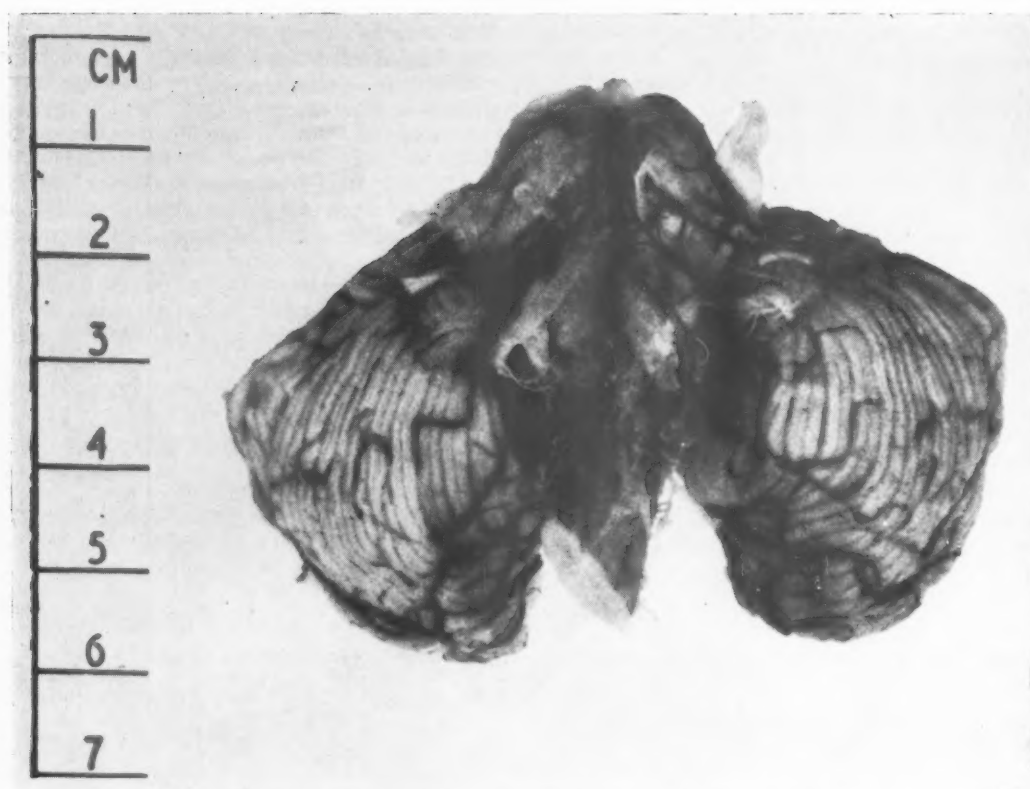FIG. 1.—Parietal cortex of M showing a small area of atrophy.

FIG. 2.—Cerebellum showing reduction of size and symmetrical areas of atrophy.

small, the folia being below the normal size and the vermis and nodule almost completely atrophic (Fig. 2). The cerebral veins and arteries were normal, however, as were the dural sinuses and meninges. No abnormality was found in the spinal cord.

Both testes were absent from the scrotum, nor could they be located in any of the usual ectopic sites; all that could be found were slight swellings on the spermatic cords near to the attachment of the gubernaculum to the scrotum. C had horseshoe kidneys but no other anatomical abnormalities. In M's case the renal cortex showed a curious yellow speckling and was of reduced width (0·2 cm.) compared with a control (0·5-0·6 cm.) of the same age. The renal pelves, ureters, bladder and penis were normal.

Histological and Enzymatic Examinations. Pieces of tissue were taken from many of M's organs and fixed in 10% formaldehyde saline. Pieces of kidney, liver, pancreas, heart and brain were 'freeze substituted' in butanol and embedded in water soluble wax; these pieces were examined histochemically for the distribution of a variety of enzymes. Portions of C's kidney were preserved at −15° C.

The kidneys of both children showed the same abnormalities to a similar degree. Deposits of calcium were visible within epithelial cells in the distal parts of the tubules and in the loops of Henle, but the exact site was difficult to define. In M's case epithelial nuclei were outlined by rings of calcium, as they may be in the metastatic nephrocalcinosis due to acidosis or alkalosis. The glomeruli in the superficial zone of the kidneys were abnormally small. Apart from their size some were normal while in others the parietal layer of Bowman's capsule was thickened (Fig. 3a and b). No such appearance was found in controls. The renal vessels appeared normal in the sections. No other abnormality was found in the remainder of the urinary tract. Sections of the lower ends of M's spermatic cords showed the epididymis to be present but none of the sections revealed any evidence of testicular tissue. The nuclei in the skin and other tissues of the older child were chromatin negative, suggesting that the genetic sex was male.

The cerebellum showed small widely spaced folia with absence of a granular layer and the presence of numerous Purkinje cells, many of them within the molecular layer (Fig. 4). All contained abundant protein when stained by the tetrazo method (Fig. 5); gliosis was scanty in the granular layer. The pons, olives, dorsal and ventral spinocerebellar tracts were normal and so were the dentate nuclei. Sections of the cerebral hemispheres revealed a deficiency of neurones in the areas of microgyria but no other abnormality was found in sections from most parts of the brain and cord. The right eye
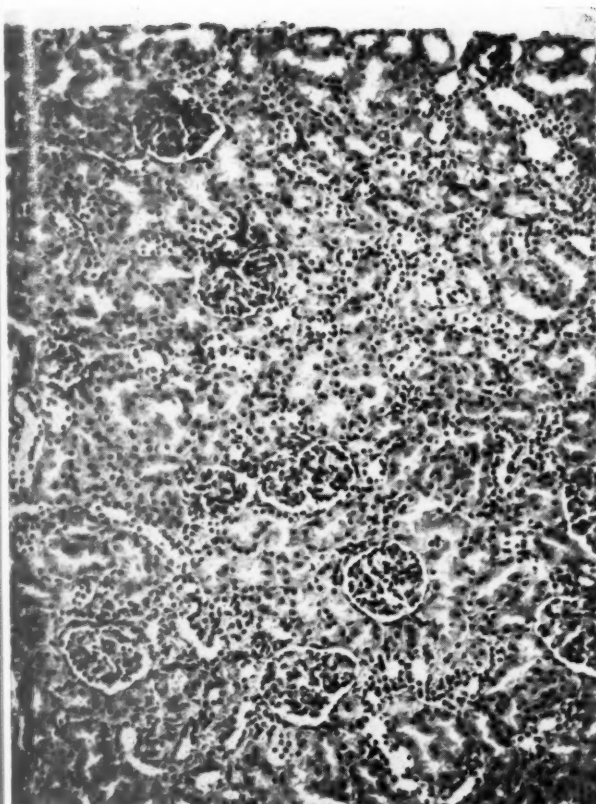
FIG. 3a.
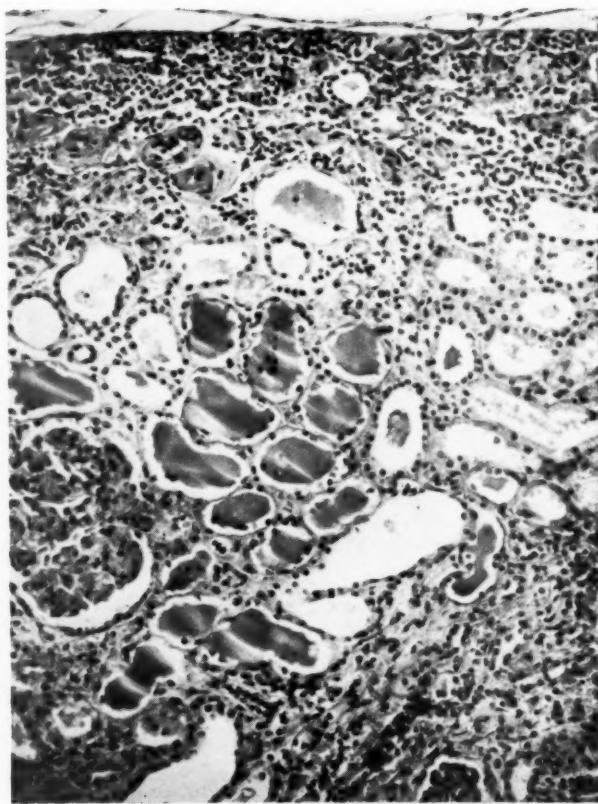
FIG. 3b.

FIG. 4.

FIG. 3a.—Section of a normal kidney from a child of the same age as M.· (H and E×115)

FIG. 3b.—Section of M.'s kidney showing a superficial zone of small fibrotic glomeruli and enlargement of an adjacent nephron. (H and E×115)
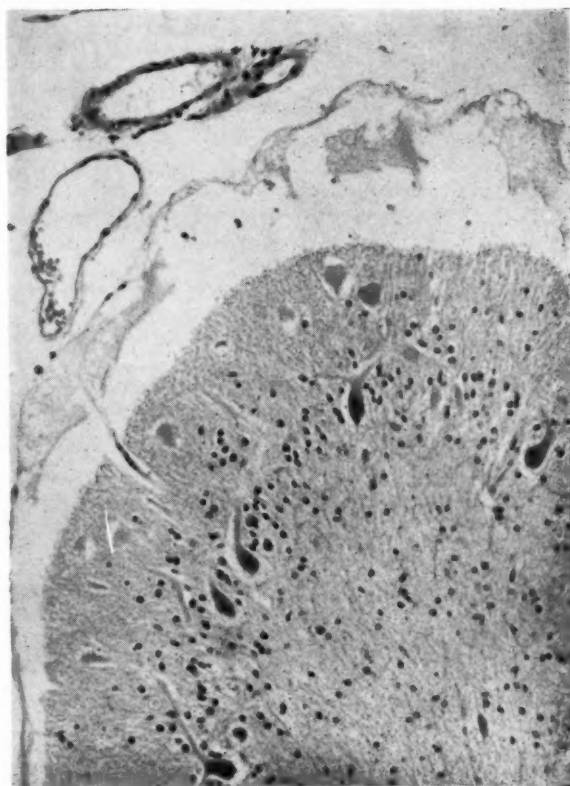
FIG. 4. Section of M.'s cerebellar cortex. Note the absence of the granul layer and the necrotic Purkinje cells near the surface. (H and E×115)

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FIG. 5.—Asteroid structures in the cerebellar cortex. Abundant protein is present in both normal and dead Purkinje cells. (Tetrazo method for protein. ×115)

was examined and some early corneal keratinization and vascularization were found but no other abnormality. These appearances in the cornea were similar to those which had been found in the cornea of the younger child C.

Premature ossification was a feature in the columns of cartilage of the epiphyseal plates at the upper end of the femur (Fig. 6) (Harris, 1933).

No abnormalities were found during the histological examinations of various parts of the gut, and plasma cells were seen in moderate numbers in the lamina propria mucosae of the intestine.

All the lobes of M's lungs contained histological abnormalities: some of the veins had agonal thrombi in them, and many of the bronchioles and alveolar ducts contained vegetable debris, indicating that some of the stomach contents had been inhaled just before death and the occasional presence of foreign body giant cells suggested that inhalation of vomit had occurred previously.

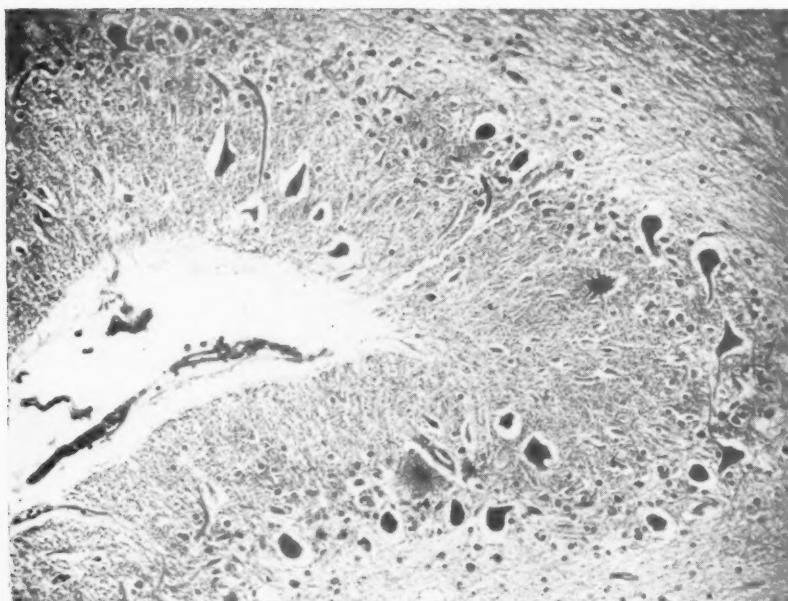Histochemical examinations of freeze substituted pieces of M's kidney, liver, pancreas and brain were made. Acid and alkaline phosphatases and non-specific

esterases were studied, but the only significant abnormality was the presence of acid phosphatase activity near to the deposits of calcium in the kidneys. An overall reduction of esterase activity was found in C's kidney associated with some spots of intense activity in certain cells. Portions of C's kidney were examined many months after the child's death for their glutaminase activity and the values found, which are given in Table 4, must be considered normal.

Discussion

The Differential Diagnosis. There is nothing really diagnostic about a disinclination for food and a failure to thrive which were the earliest causes of anxiety. Recognition of the mental retardation, corneal opacities, nystagmus and photophobia came later, as did the severe reduction in the plasma bicarbonate, and

TABLE 4

THE GLUTAMINASE ACTIVITY OF THE KIDNEY OF THE YOUNGER CHILD AND OF A CONTROL OF ABOUT THE SAME WEIGHT

(see Radde and McCance, 1959)

	mg. NH$_3$/100 mg. dry matter/hour	
	Patient	Control
Without added glutamine	103	84
With added glutamine ..	353	215
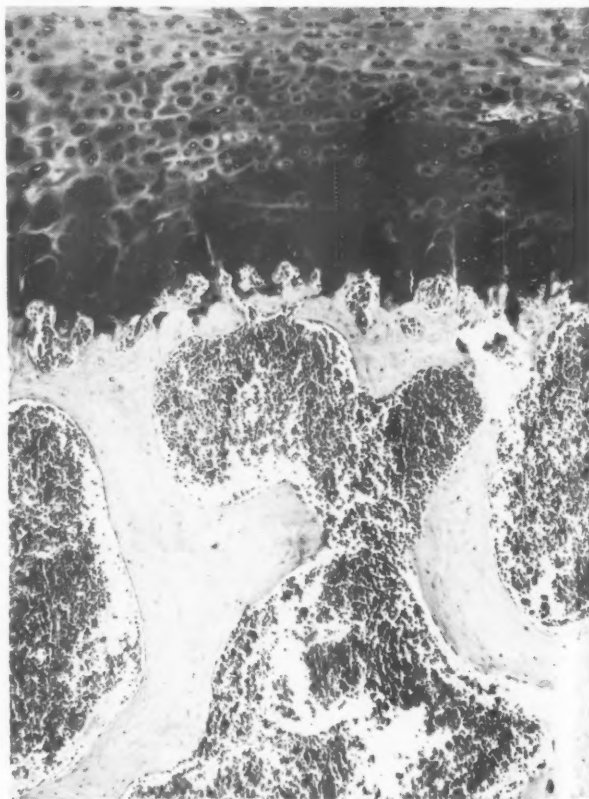
FIG. 6.—Section of M.'s upper femoral epiphyseal plate to show the arrest of growth. (H and E ×45)

the raised blood urea. The highly acid urines, however, separate M and C from the children described by Lowe *et al.* (1952), and by Royer and Prader (1957) because all of the latter were apparently unable to acidify the urine and therefore were correctly diagnosed as cases of renal tubular acidosis (Stapleton, 1949; Doxiadis, 1952; Wilkinson, 1954). They were also excreting large amounts of organic—probably amino acids—in their urine (Jackson and Linder, 1953; Piel, 1957; Jonxis, 1957; Mudge, 1958). The present children were not, and the amino acid patterns of the serum and C.S.F. of the elder boy (the only one whose C.S.F. was tested) were also normal. These findings were taken at the time to rule out cystinosis, and this was again excluded by chemical and histochemical tests made on the tissues after death. Other records which were studied in making the differential diagnosis were those of Goldbloom *et al.* (1957). The disease in their cases had a different age of onset, and the patients suffered from nerve-deafness and a lesion described as chronic interstitial pyelonephritis. These syndromes, like the present one, may be familial (Cooke and Kleeman, 1950; Rendle-Short, 1953; Schreiner, Smith and Kyle, 1953; Foss, Perry and Wood, 1956; Wrong and Davies, 1959).

It is frequently stated that patients with renal tubular acidosis are unable to excrete ammonia (Lowe *et al.*, 1952; Lowe and Smith, 1955; Albright, Burnett, Parson, Reifenstein and Roos, 1946; Albright, Consolazio, Coombs, Sulkowitch and Talbott, 1940; Baines, Barclay and Cooke, 1945; Boyd and Stearns, 1942; McCune and Pray, 1940; Piel, 1957; Debré *et al.*, 1955; Debré, Royer and Lestradet, 1956; Royer and Prader, 1957). Some authors have considered that there is no real interference with the formation of ammonia in this disease (Gabrielsen, 1954; Stapleton, 1949; Latner and Burnard, 1950; Wrong and Davies, 1959). With this the information given in the literature is really in agreement (see Table 2), although the patients may have been said to be unable to excrete ammonia. The patients of Lowe *et al.* (1952), for example, had perfectly normal NH_3/NH_3+titratable acidity ratios in their urine; the figures given averaged over $0 \cdot 6$, and there is no evidence that their kidneys could not have produced NH_3 in normal measure if there had been any way of putting them under test by making the urine acid. There is nothing in renal tubular acidosis comparable to the findings in these two children in whose urines the ammonia formed less than 30% of the ammonia $+$ the titratable acidity even when the pH had been very low for weeks. This is the state of affairs

originally described by Palmer and Henderson (1915) and Henderson and Palmer (1915), who reported that, in some patients with advanced chronic glomerular nephritis, the NH_3/NH_3+titratable acidity ratios were subnormal. These findings have been confirmed by several investigators and the whole subject brought up to date by Schwartz *et al.* (1959) and by Wrong and Davies (1959). M was investigated when the concentration of urea in his plasma was still only 100 mg./100 ml. or less, and his concentrating power reasonably good. The kidneys of both children were examined after death and neither of them had lesions in any way resembling chronic glomerular nephritis as had those of the children with a somewhat similar syndrome reported by Goldbloom *et al.* (1957). It was concluded therefore that a feature of our cases was a rather specific failure of the kidney to excrete ammonium ions—see Wrong and Davies (1959). Talbot, Sobel, McArthur and Crawford (1952) have described one patient who appears to have had a specific renal deficiency in the excretion of ammonia, but no others seem to have been recorded. Talbot *et al.* (1952) were interested in such patients mainly because the lesion might lead to the excretion of so much fixed base, particularly of calcium, that the patients developed osteomalacia. They therefore described their case in the section of their book dealing with the parathyroid glands, and the authors have informed us that contact with this patient has been lost.

The Normality of the Titratable Acidity. The excretion of a subnormal percentage of the total surplus anions as ammonium salts might have been caused by a very high titratable acidity in the urine due to the excretion of abnormal buffer substances. There was no evidence of this in M or C, for the amino acids in the urine were normal in amount and type, and the quantities of phosphates excreted in the urine were enough to account for the customary percentage of the titratable acidity. Thus the average percentage for six normal adults was 65 after five days on ammonium chloride and M's average over three days, before being treated, was 75%. The pH of the urines both in the adults and in M ranged from $4 \cdot 6$-$4 \cdot 9$. There is no evidence, therefore, that the titratable acidity was unusually magnified in quantity or form or that the $NH_3 \times 100/NH_3+$titratable acidity was abnormal for this reason.

The Ammonia Coefficient. M's failure to excrete ammonia suggested an investigation of the percentage of his total nitrogen excreted as ammonium

salts (the ammonia coefficient). This was very low, particularly when the pH of the urine was taken into account. Thus, out of a group of eight urines all with pH between $4 \cdot 6$ and $4 \cdot 9$, M's ammonia coefficient averaged only $1 \cdot 6$. The ammonia coefficient of the six normal adults averaged $3 \cdot 5$ when their urines had an average pH of $6 \cdot 0$, and the ammonia coefficient rose to $11 \cdot 5$ after five days on ammonium chloride.

The Nature of the Lesion. The lesions as a whole should probably be regarded as developmental failures, but the cerebral and cerebellar findings are unusual. Agenesis of the cerebral and cerebellar cortices usually leads to degeneration of the Purkinje and granular cells and extensive atrophy of the cerebral cortex (Norman, 1958). Furthermore the vermis and flocculi are usually normal, which they certainly were not in this case (Fig. 2). The cortical and cerebellar lesions appear not to have been neurologically associated since the pontine and dentate nuclei were normal, and no abnormality was detected in the cerebral peduncles or in the thalamus.

The cerebellar lesion is probably best considered as a developmental failure or early atrophy of cells in the granular layer, and if this is so the conspicuous involvement of the vermis is unusual (Ule, 1952). The suggestion is supported however by the asteroid like brushwork of fibres derived from Purkinje cells (Fig. 5); and another finding in favour is that the inferior olives were normal. The aetiology of cerebellar granular atrophy is in some cases familial (Norman, 1940) and usually associated with severe mental defect, as it was in this boy.

Both testes were absent and the case might, therefore, be classified as belonging to Klinefelter's syndrome in which mental abnormality, feeble-mindedness and idiocy have been described by Ferguson-Smith (1958). Total absence of both testes is a decidedly rare anomaly. The finding of chromatin positive (Barr positive) nuclei neither supports nor refutes a diagnosis of Klinefelter's disease.

The other conspicuous abnormality lay in the kidneys, where the thin rind of small cortical glomeruli again suggests development failure, though it is just possible that some of the appearances might have been the result of pyelonephritis. The deposits of calcium and the occasional paratubular granulomata were probably sequelae of the metabolic disturbances which were such a feature during life. The high concentration of urea in the serum of both children indicates that their glomerular filtration rates were low. Determinations of M's endo-genous creatinine clearance were found to be $0 \cdot 7$ ml / kg./min. on December 17, 1957. Some lowering of the glomerular filtration rate in the absence of much, if any, histological sign of glomerular destruction is also in keeping with the large numbers of small and apparently undeveloped glomeruli in the peripheral parts of the cortex. It is just possible that the failure to excrete ammonium was functionally connected with these low glomerular filtration rates and not with any tubular lesion (Wrong and Davies, 1959), but M's glomerular filtration rates were not low enough in the early stages of his disease for this to be a very satisfactory explanation.

Summary

The following syndrome has been defined following its investigation in two brothers whose parents were unrelated and healthy.

Little desire for food from birth; failure to grow and thrive; later, vomiting and sporadic attacks of diarrhoea.

Corneal opacities, partial blindness and nystagmus.

Mental retardation, intention tremor and (in one sibling) convulsions.

Serum: 'total CO_2' very low, sodium low normal, potassium over normal, phosphorus normal, urea in the early stages 80-100 mg./100 ml., terminal stages 270 mg.

Urine: always sterile, highly acid. Sp. gr. 1017 or more in the early stages. $NH_3 \times 100/NH_3 + $tit-ratable acidity abnormally low, but no reduction in the glutaminase activity of the kidney *in vitro*.

Normal response to acetazolamide (one test).

Death from progressive renal failure.

Post mortem: conspicuous structural abnormalities in the brain, slight keratinization and vascularity of the cornea. Some calcification of the kidney. Many small (perhaps undeveloped) glomeruli in the periphery of a narrow cortex and no testes.

REFERENCES

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C. and Roos, A. (1946). Osteomalacia and late rickets. *Medicine (Baltimore)*, 25, 399.
——, Consolazio, W. V., Coombs, F. S., Sulkowitch, H. W. and Talbott, J. H. (1940). Metabolic studies and therapy in a case of nephrocalcinosis with rickets and dwarfism. *Johns Hopk. Hosp. Bull.*, 66, 7.
Baines, G. H., Barclay, J. A. and Cooke, W. T. (1945). Nephrocalcinosis associated with hyperchloraemia and low plasma bicarbonate. *Quart. J. Med.*, n.s., 14, 113.

Boyd, J. D. and Stearns, G. (1942). Concomitance of chronic acidosis with late rickets. *Amer. J. Dis. Child.*, **64**, 594.

Cooke, R. E. and Kleeman, C. R. (1950). Distal tubular dysfunction with renal calcification. *Yale J. Biol. Med.*, **23**, 199.

Davies, B. M. A. and Yudkin, J. (1952). Studies in biochemical adaptation. The origin of urinary ammonia as indicated by the effect of chronic acidosis and alkalosis on some renal enzymes in the rat. *Biochem. J.*, **52**, 407.

Debré, R., Royer, P. and Lestradet, H. (1956). Les insuffisances congénitales du tubule rénal chez l'enfant. *Sem. Hôp. Paris* 32, 235/p7-254/p26.

—, —, — and Straub, W. (1955). L'insuffisance tubulaire congénitale avec arriération mentale, cataracte et glaucome (syndrome de Lowe). *Arch. franç. Pédiat.*, **12**, 337.

Doxiadis, S. A. (1952). Idiopathic renal acidosis in infancy. *Arch. Dis. Childh.*, **27**, 409.

Ferguson-Smith, M. A. (1958). Chromatin-positive Klinefelter's syndrome (primary microrchidism) in a mental-deficiency hospital. *Lancet*, **1**, 928.

Foss, G. L., Perry, C. B. and Wood, F. J. Y. (1956). Renal tubular acidosis. *Quart. J. Med.* n.s., **25**, 185.

Gabrielsen, L. H. (1954). Idiopathic renal acidosis. *Acta paediat. Stockh.*, **43**, 198.

Goldbloom, R. B., Fraser, F. C., Waugh, D., Aronovitch, M. and Wiglesworth, F. W. (1957). Hereditary renal disease associated with nerve deafness and ocular lesions. *Pediatrics*, **20**, 241.

Harris, H. A. (1933). *Bone Growth in Health and Disease*, p. 6 *et seq.* Oxford University Press, London.

Henderson, L. J. and Palmer, W. W. (1915). On the several factors of acid excretion in nephritis. *J. biol. Chem.*, **21**, 37.

Jackson, W. P. U. and Linder, G. C. (1953). Innate functional defects of the renal tubules, with particular reference to the Fanconi syndrome. *Quart. J. Med.* n.s., **22**, 133.

Jonxis, J. H. P. (1957). Aminoacidurie. *Ergebn. inn. Med. Kinderheilk* n.s., **8**, 169.

Latner, A. L. and Burnard, E. D. (1950). Idiopathic hyperchloraemic renal acidosis of infants (nephrocalcinosis infantum). Observations on the site and nature of the lesion. *Quart. J. Med.* n.s., **19**, 285.

Linder, G. C. (1927). The effect of mineral acid on acid-base regulation in health and in nephritis. *Quart. J. Med.*, n.s. **20**, 285.

Lowe, C. U. and Smith, R. T. (1955). Pyruvic aciduria in a patient with organic aciduria. *Helv. paediat. Acta*, **10**, 220.

—, Terry, M. and MacLachlan, E. A. (1952). Organic aciduria, decreased renal ammonia production, hydrophthalmos and mental retardation. *Amer. J. Dis. Child.*, **83**, 164.

McCune, D. J. and Pray, L. G. (1940). Nephrocalcinosis with chronic tetany. *Amer. J. Dis. Child.*, **60**, 993.

Marriott, W. M. and Howland, J. (1918). The influence of acid phosphate on the elimination of ammonia in the urine *Arch. intern. Med.*, **22**, 477.

Mudge, G. H. (1958). Clinical patterns of tubular dysfunction. *Amer. J. Med.*, **24**, 785.

Norman, R. M. (1940). Primary degeneration of the granular layer of the cerebellum: an unusual form of familial cerebellar atrophy occurring in early life. *Brain*, **63**, 365.

—— (1958). *In* Greenfield, J. G., Blackwood, W., McMenemey, W. H., Meyer, A. and Norman, R. M. (1958). *Neuropathology*, p. 339 *et seq.* Arnold, London.

Palmer, W. W. and Henderson, L. J. (1915). A study of the severa factors of acid excretion in nephritis. *Arch. intern. Med.*, **16**, 109.

Piel, C. F. (1957). Diseases of the renal tubules in childhood. *Pediatrics*, **20**, 337.

Radde, I. C. and McCance, R. A. (1959). Glutaminase activity of the foetal membranes and kidneys of pigs. *Nature (Lond.)*, **183**, 115.

Rector, F. C., Seldin, D. W. and Copenhaver, J. H. (1955). The mechanism of ammonia excretion during ammonium chloride acidosis. *J. clin. Invest.*, **34**, 20.

Rendle-Short, J. (1953). Idiopathic renal acidosis in twins. Alkalosis resulting from overdosage of a citrate mixture. *Arch. Dis. Childh.*, **28**, 55.

Royer, P. and Prader, A. (1957). Les insuffisances congénitales du tubule rénal chez l'enfant. 16e Congrès des Pédiat. Langue Franç, **1**, 263.

Ryberg, C. (1948). On the formation of ammonia in the kidneys during acidosis. *Acta physiol. scand.*, **15**, 114.

Schreiner, G. E., Smith, L. H. and Kyle, L. H. (1953). Renal hyperchloremic acidosis. *Amer. J. Med.*, **15**, 122.

Schwartz, W. B., Hall, P. W., Hays, R. M. and Relman, A. S. (1959). On the mechanism of acidosis in chronic renal disease. *J. clin. Invest.*, **38**, 39.

Van Slyke, D. D., Linder, G. C., Hiller, A., Leiter, L. and McIntosh, J. F. (1926). The excretion of ammonia and titratable acid in nephritis. *Ibid.*, **2**, 255.

Stapleton, T. (1949). Idiopathic renal acidosis in an infant with excessive loss of bicarbonate in the urine. *Lancet*, **1**, 683.

Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D. (1952). *Functional Endocrinology from Birth through Adolescence.* Harvard University Press, Cambridge, Mass.

Ule, G. (1952). Kleinhirnrindenatrophie vom Körnertyp. *Dtsch. Z. Nervenheilk.*, **168**, 195.

Wilkinson, R. H. (1954). Some metabolic disorders. In *Recent Advances in Paediatrics*, ed. by D. Gairdner, p. 368. Churchill, London.

Wrong, O. and Davies, H. E. F. (1959). The excretion of acid in renal disease. *Quart. J. Med.* n.s., **28**, 259.

SIRENOMELIA AND MONOMELIA
WITH RENAL AGENESIS AND AMNION NODOSUM

BY

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Interest has recently been directed towards sympodia, a foetal malformation better known by the synonyms sirenomelia, sympus dipus or mermaid foetus. This malformation consists of more or less complete fusion of the lower limbs to form a single extremity.

Less frequently reported is the condition described by Ballantyne (1904) as monopodia, in which there is a single lower extremity which shows no indication that it has been derived from the fusion of two lower limbs. For this abnormality we prefer the term monomelia.

Severe dysplasia of the foetal urinary tract is apparently an invariable accompaniment of sirenomelia and monomelia. Despite the considerable number of cases described in the literature scant attention has been paid to certain other associated features in the foetus. Only occasionally is reference made to the liquor amnii, and there are no previous histological studies of the placental membranes.

Case Reports

Case 1. The mother, aged 35, para. 9, gravida 10, was perfectly well throughout her pregnancy. She was uncooperative and refused ante-natal care. At 41 weeks she went into spontaneous labour and was delivered of a male foetus weighing 1,804 g. as a breech presentation. No doctor was present and consequently no observations were made as regards the liquor amnii. There was no history of the membranes ever having ruptured.

There was no consanguinity of the parents, nor maternal illness during the antepartum period.

AUTOPSY FINDINGS. The foetus showed a single midline lower extremity measuring approximately 16 cm. which terminated in a stump with no attached digits (Fig. 1). The face presented the characteristics usually associated with renal agenesis; the ears were large, flattened and low set; the nose flattened at the tip; the space between the eyes increased; the chin receding and the epicanthic folds prominent (Potter facies). The right hand was large, clumsy and spade-like; the left

had only two digits. The anus was imperforate. There were no external genitalia.

The only abnormalities noted on internal examination were small hypoplastic lungs and total absence of both kidneys. Two testes were found in the pelvis.

FIG. 1.—Case 1. Monomelic foetus showing large spade-like hands.

Case 2. The mother, aged 19, para 0, was perfectly well throughout her pregnancy. Although there was no doubt as to the date of her last menstrual period the uterus was found to be consistently small for the estimated period of gestation. At the forty-second week of her

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pregnancy she went into spontaneous labour and was delivered of a stillborn male foetus, weighing 1,850 g., as a breech presentation. The membranes were intact up to the time of delivery and no escape of liquor was noticed.

There was no consanguinity of the parents, nor any history of maternal illness during pregnancy.

AUTOPSY FINDINGS. The foetus showed features identical with Case 1, with a single lower extremity, Potter facies, large spade-like hands, absence of external genitalia and anal atresia.

Internal examination showed that the kidneys were absent and the lungs typically hypoplastic. Two testes were found in the pelvis.

Case 3. The clinical case records could not be traced and consequently no maternal history was available.

AUTOPSY FINDINGS. The foetus weighed 1,200 g. and presented the typical deformity of sirenomelia, there being a single fused lower limb terminating in a foot on which there were two great toes (Fig. 2). The foetus

weighing 2,300 g. The membranes were intact up to the time of delivery, and no escape of liquor was noticed.

There was no consanguinity of the parents. The only previous maternal illness was tuberculosis of the bones during childhood.

AUTOPSY FINDINGS. The foetus was a typical example of sirenomelia, with a single lower limb composed of elements of two fused limbs. The foetus showed the typical Potter facies, and the hands were large and spade-like (Fig. 3). There were no external genitalia and the anus was imperforate.

Internal examination revealed small hypoplastic lungs, complete absence of both kidneys, an enterogenous cyst

FIG. 2.—Case 3. Sirenomelic foetus with exomphalos.

FIG. 3.—Case 4. Sirenomelic foetus showing Potter facies and large spade-like hands.

showed the Potter facies, large spade-like hands, imperforate anus and no external genitalia.

There was a large exomphalos which contained the greater part of the abdominal viscera. The kidneys were absent and the internal genitalia could not be found. The lungs were hypoplastic.

Case 4. The mother was a primagravida who had excessive vomiting during early pregnancy. The uterus was found to be consistently small for the period of gestation. At 34 weeks she had an episode of vaginal bleeding and about this time also developed ankle oedema. At 44 weeks she went into spontaneous labour and was delivered of a female foetus as a vertex L.O.A.

on the posterior abdominal wall, normal fallopian tubes and ovaries and a vestigial uterus but no vagina.

Placental Examination

Case 1. The placenta weighed 350 g. The foetal surface and membranes were found to be studded with numerous small whitish nodules approximately 1-2 mm. in diameter. These were firmly adherent to the amnion and presented the appearance typical of amnion nodosum. The maternal surface of the placenta showed no abnormality. The umbilical cord contained three vessels.

Microscopical examination of the membranes confirmed the presence of amnion nodosum typified by aggregations of epidermal squames embedded on the surface of the amnion. The placental tissue itself was normal.

Cases 2 and 3. No note was made in the macroscopical examination of any abnormal appearance of the amnion. Retrospective microscopical examination of sections of the membranes revealed the characteristic lesion of amnion nodosum.

Case 4. The placenta was not submitted for examination.

Radiological Report

Radiological examination of the monomelic foetuses (Cases 1 and 2) revealed the single lower limb to consist of a femur and part of a tibia (Fig. 4).

present, but there were irregular areas of ossification in the site usually occupied by these bones. There were no tarsal bones but a 'bifid' single foot with irregular metatarsal and phalangeal bones.

Discussion

Babies born with either sirenomelia or monomelia are either stillborn or survive only a few hours. This fact was noted by Ballantyne (1904) and, although he was not clear as to the cause, he suggested that early death might be associated with the frequent absence of kidneys.

In the present series of cases kidneys were entirely absent, and the pulmonary hypoplasia associated with renal agenesis was a constant feature. Kidneys were, however, noted in a report by Hendry and Kohler (1956), but it is interesting that there was in this case a complete atresia of the urethra.

FIG. 4.—Radiograph of monomelic foetus showing lower extremity to be composed of a femur and part of a tibia.

FIG. 5.—Radiograph of sirenomelic foetus demonstrating fusion of the two lower limbs.

The other abnormalities included hemivertebrae of the dorsal spine.

In the sirenomelic foetuses (Cases 3 and 4) there was fusion of the lower limbs with two femora and two deformed tibia (Fig. 5). No fibulae were

The excellent illustrations of sirenomelia and monomelia by Ballantyne (1904), Foulkes and McMurray (1954), Hendry and Kohler (1956) and Jolly and Lamont (1958) show what is now regarded as the characteristic facial appearance first described

by Potter (1946a and b) in association with renal agenesis. The illustrations of these authors also show the large flattened and clumsy appearance of the hands described by Bain and Scott (1960) in connexion with severe urinary tract dysplasia. Although such features have not been generally recognized as associated with sirenomelia and monomelia, Fritzsche (1955) noted the presence of Potter facies in a case of monomelia.

References to the volume of liquor amnii are generally vague and there appears to be no definite observation of oligohydramnios. Obstetrical histories were obtained in three of the present four cases. The salient points in these histories were a uterus smaller than usual for the expected period of gestation, membranes intact until the time of delivery, and no note of the escape of liquor amnii.

These facts are highly suggestive of oligohydramnios, but proof of the absence of liquor was obtained by placental examination. In three out of the four cases the placentae were examined histologically and amnion nodosum was found to be present. As shown by Scott and Bain (1958) this lesion, which consists of plaques of epithelial squames on the surface of the amnion, is found only in association with oligohydramnios.

It is of interest that Resnick (1945) noted that hydramnios, usually expected in the presence of foetal malformations, was not present in association with sirenomelia. He quotes a case described by Bauereisen (1905). This was a twin pregnancy in association with hydramnios, one of the twins being a true sympodia and the other having anal atresia but showing absence of only one kidney. It is highly probable that the hydramnios was in fact limited to the foetus with anal atresia.

Two out of the four present foetuses were delivered as breech presentations. This abnormal presentation, frequently noted in previously reported cases, is known to be favoured by the absence of foetal micturition.

Little is known as regards the aetiology of sirenomelia or monomelia, but several theories have been put forward including the suggestion that oligohydramnios is one of the causes. The oligohydramnios is obviously secondary to an embryonic defect involving the foetal kidneys or urinary tract, and although it can account for the appearances produced in the face and hands, it is unlikely to produce fusion of the lower limbs or monomelia. Absence of one umbilical artery has been cited as an aetiological factor on the assumption that it impairs blood supply to the lower limbs. However, absence of one umbilical artery is seen frequently in babies with varied congenital malformations and occasionally in apparently normal infants. The cause of these malformations could be either genetic damage or injury to the developing embryo by factors as yet unknown.

Summary

Two cases of sirenomelia and two of monomelia have been described in view of additional features not mentioned in previous reports. The Potter facies, large spade-like hands and pulmonary hypoplasia were present in all four cases. Examination of the placentae in three cases revealed the lesion of amnion nodosum, a finding indicative of oligohydramnios. Oligohydramnios was in fact noted clinically in two instances.

We conclude that severe urinary tract dysplasia, such as renal agenesis or complete urethral atresia, and its associated foetal and placental changes are a constant finding in sirenomelia and monomelia.

REFERENCES

Bain, A. D. and Scott, J. S. (1960). Renal agenesis and severe urinary tract dysplasia. *Brit. med. J.*, 1, 841.
Ballantyne, J. W. (1904). *Manual of Antenatal Pathology and Hygiene.* Green, Edinburgh.
Bauereisen, A. (1905). IX. Sitzung Fränkische Gesellschaft für Geburtshilfe und Frauenheilkunde. Erlangen. *Münch. med. Wschr.*, 52, 721.
Foulkes, J. F. and McMurray, J. (1954). A case of sympodia. *J. Obstet. Gynaec. Brit. Emp.*, 61, 827.
Fritzsche, F. (1955). Über eine sirenoide Missbildung mit Hinweis auf Anomalien der Gesichtsbildung. *Zbl. allg. Path. path. Anat.*, 94, 170.
Hendry, D. W. and Kohler, H. G. (1956). Sirenomelia ('Mermaid'). *J. Obstet. Gynaec. Brit. Emp.*, 63, 865.
Jolly, H. and Lamont, E. M. (1958). Sirenomelia: Sympus dipus ('Mermaid'). *Arch. Dis. Childh.*, 33, 226.
Potter, E. L. (1946a). Bilateral renal agenesis. *J. Pediat.*, 29, 68.
—— (1946b). Facial characteristics of infants with bilateral renal agenesis. *Amer. J. Obstet. Gynaec.*, 51, 885.
Resnick, L. (1945). A case of simpus dipus. *J. Obstet. Gynaec. Brit. Emp.*, 52, 515.
Scott, J. S. and Bain, A. D. (1958). Amnion nodosum. *Proc. roy. Soc. Med.*, 51, 512.

THE ASSOCIATION OF
SIRENOMELIA WITH POTTER'S SYNDROME

BY

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The Greeks considered congenital deformities to be of divine origin and eventually these monsters were thought to indicate a divine warning of some future calamity and the infant and even the mother were sacrificed to propitiate the gods (Glenister, 1957). The sympodial deformity has been recognized from earliest times and may well have given rise to the myth of the siren. The legendary monster of the Lybian desert, the sciapod, or shadow foot, described by both Herodotus and Pliny (Fig. 1), may well have had a similar origin. This man used his foot as a sunshade when resting. Early writers showed a remarkable degree of wishful thinking and poetic licence in their descriptions of

FIG. 1.—The sciapod or shadow foot. This carving from a fourteenth century bench end in the nave of Dennington Church, Suffolk, shows a fused lower limb and a large foot with 10 toes. Unlike the true sympodial limb, the knees flex posteriorly.

FIG. 2.—The sympodial foetus described and illustrated by Thomas Bartholin. Note the presence of mammary glands and webbed hands.

the sympodial monster. Bartholin (1654) even reported mammary glands and webbed fingers in his case (Fig. 2).

Although the sympodial deformity is a rare condition a number of cases have been reported in the literature, and the subject has been reviewed by Kampmeier (1927) and Hendry and Kohler (1956).

The case described in this report shows the association of the abnormality with the syndrome described by Potter (1946) of renal agenesis, hypoplasia of the lungs and a typical facies. This association does not seem to have been reported in any of the cases of sympodia described up to the present, although it is probable that the association is common.

The anatomical and embryological aspects of this case have been described elsewhere (Bearn, 1960).

Case Record

A sympodial foetus, stillborn, and fixed in formalin, was made available for study.

FIG. 4.—The face of the sympodial foetus showing the features typical of Potter's syndrome.

Obstetric History. The mother was married, aged 22 years and had given birth two years previously to a normal 40 week infant, which had died before the arrival of the midwife. During the second pregnancy, there was no history of any abnormality and no history of oligohydramnios was reported. Labour was at 40 weeks and was uneventful, lasting six hours. She was group O, Rhesus positive. After the birth of the abnormal child, the blood of both the mother and father was again checked, and no ABO or other incompatibility was found.

External Examination. The specimen (Fig. 3) was a human foetus of indeterminate sex, with a 2nd degree sympodial deformity, weighing 2lb. 1oz.

The face (Fig. 4) showed all the features first described by Potter (1946) in association with bilateral renal agenesis: flattening of the nose, recession of the chin, soft flat ears, with apparent absence of the cartilage, and low positioning of the ears on the side of the head. The eyes showed a wide intra-ocular distance, and prominent epicanthic folds, forming a wide semicircle on each side of the nose and covering each medial palpebral commissure.

The upper limbs and thorax were normal. The pelvis was reduced in size and no external genitalia could be

FIG. 3.—The sympodial foetus showing the fused lower limb, with 10 toes, the two little toes fused and big toes on outer sides of foot.

found. There was a blind pit dorsally at the lower end of the trunk which could have represented an imperforate anus, otherwise no sign of an opening of the anus or urethra could be found.

The lower limbs were joined together, the site of the fusion being along the post-axial borders of the limbs as far as the tips of the little toes. The soles of the feet faced anteriorly. Ten toes were present, the two outermost toes being the big toes, and the two little toes being partially fused together in the midline. The two patellae were felt on the postero-lateral aspect of the knee, and the joint could be flexed anteriorly.

FIG. 5.—Radiograph showing the double skeleton of the single limb, with the fibulae lying internal to the tibiae.

Radiological Examination of the Lower Limb. The radiograph showed no abnormalities in the upper limbs, head and trunk (Fig. 5). Six lumbar vertebrae and the first two pieces of the sacrum were present, the remaining three pieces and the coccyx being absent. The ilium was present on each side, and the pubis was represented by a fused midline bone. The radiograph of the fused limb showed the presence of both femora, and both tibae and fibulae, their relative positions being reversed. Two tarsal bones, and the metacarpals and phalanges, were present.

Internal Examination. The internal structures of the head and neck were normal. The heart was normal,

but the lungs were markedly underdeveloped and failed to fill the thoracic cavity, this hypoplasia being more marked on the left side, and the pleural cavities were filled with fluid. The size of the thoracic cavity was normal. The alimentary tract was normal as far as the rectum, which ended as a blind stump. The liver, spleen and pancreas were normal, the left adrenal only was present, and was flattened antero-posteriorly and the kidneys and ureters were absent except for a small mass on the left side below the adrenal gland, which was shown histologically to contain some renal tissue. The pelvic cavity was very shallow and contained none of its normal contents. The urogenital tract was absent and the external genitalia could not be found. The testes were present in each iliac fossa. Only the right umbilical artery was found.

The Skeleton and Musculature of the Pelvis and Lower Limb. The main muscle groups of the pelvis and the fused limb were all present and with very few exceptions, even the individual muscles of each group could be identified. The muscles of the gluteal region were present and were in their normal positions, the greater trochanters being in a more posterior position than usual. These two regions were in much the same relative positions as in the normal foetus. The upper two-thirds of the thigh showed only a partial reversal from the normal position, and each patella was identified on the postero-lateral aspect of the thigh. From the knee joints downwards, the limbs showed a complete reversal of position, and flexion of the knee joint was in an anterior direction. The tibia and fibula on each side were reversed, the two fibulae being adjacent to each other on the internal aspects of the tibiae. The femoral, obturator and sciatic nerves were identified in each limb supplying their respective muscle groups. The details of the muscles and skeleton have been reported in an earlier paper (Bearn, 1960).

Discussion

The condition of sympodial foetus is most uncommon. Ballantyne (1898) collected only 120 cases in the literature; Kampmeier (1927) collected 51 more cases, including one of his own. Since then occasional reports of individual cases have appeared in the literature: Dreyfuss (1928), Newbill (1941), Resnick (1945), Dodek and Friedman (1950), Potter (1952), Foulkes and McMurray (1954), Jones and Lee (1955), Hendry and Kohler (1956), Jolly and Lamont (1958).

Sympodial foetuses are classified into three degrees, depending on the completeness of the fusion of the two limbs, Förster (1861, 1865).

(1) **Symelia apus.** No feet are present, the limbs are completely fused into one single limb. One femur and one tibia are present.

(2) **Symelia unipus.** One foot is present, this being a partial fusion of the two feet. Up to

ten toes may be found, the little toes being fused together and the plantar surface of the foot facing anteriorly. Two femora and two tibiae and fibulae are present, the latter bone being medial to each tibia. The main muscle groups can usually be identified.

(3) **Symelia bipus.** Two feet are present, giving the appearance of fins—hence the name 'mermaid' foetuses for this abnormality. The fusion of the limbs extends only as far as the ankles, and the muscles of the two limbs are all present.

The position of the fused limb in this condition is of great embryological interest, as it demonstrates a persistence of the early foetal unrotated position of the limb. The normal lower limb undergoes internal rotation, so that the post-axial border and digit of the little toe become lateral and the ventral surface faces posteriorly. In the sympodial deformity the developing limb buds are fused from the start along their post-axial borders and rotation is therefore impossible.

Causation of the Sympodial Deformity. This has been discussed in detail elsewhere (Bearn, 1960). Bolk (1899) and Ballantyne (1904) both suggested that the defect was primarily a failure of development of the caudal segments at a very early stage before the limb buds form. Wolff (1936) has produced the sympodial deformity in the chick by destroying the caudal end of the early embryo with x-rays. This work of Wolff (1936) confirms experimentally the suggestions that the primary defect in the sympodial deformity is one of the caudal region of the embryo, but how this defect is produced in the early human embryo is not known. The defect must also involve the presumptive area for the urogenital tract, as these structures including the kidney do not develop in the human monster.

The Association of Sympodia with Potter's Syndrome. The face of this foetus (Fig. 4) shows all the characteristics, first described by Potter (1946), found in cases of renal agenesis. 'The most striking feature consists of an increase in width between the eyes and the presence of an unusually prominent fold arising at the inner canthus of each eye. The fold sweeps downward and laterally to form a wide semicircle under the inferior medial aspect of each orbital space. Other changes . . . are a flattening and slight broadening of the nose, an unusually receding chin and large low-set ears which have proportionately little cartilage.' Although this facies has not been reported in any of

the papers on sympodia published since Potter's paper in 1946, it is likely that most sympodial foetuses show these features, in view of the usual absence of renal tissue in this deformity. In the paper by Hendry and Kohler (1956) Fig. 6 shows some of the features of this facies, and in the paper by Jolly and Lamont (1958) Fig. 1 shows most of the characteristics, including the epicanthic fold. However, the specimen described by Jones and Lee (1955), now preserved in the Anatomy Department of the Middlesex Hospital Medical School, shows a normal facies in spite of complete absence of renal tissue. Hilson (1957) has shown that abnormalities of the ears, somewhat similar to those seen in Potter's syndrome, occur in other malformations of the urinary tract, such as bifid ureter, or absence of one kidney.

It is not yet possible to explain the association of the typical facies described by Potter (1946) occurring in renal agenesis and in cases of sympodia.

It is possible that the peculiar facies may be explained by the compression of the head by the uterine wall, secondary to the oligohydramnios which is usually present both in sympodia and in cases of renal agenesis without gross abnormalities of the lower limbs.

The flattening of the nose, the receding chin and the flattened malpositioned ears could all be due to a mechanical pressure effect on the developing head.

The presence of oligohydramnios was not reported in the obstetric history of this patient, although it is often noticed in both sympodia and renal agenesis, and it is probable that there is a direct relation between the renal agenesis and the oligohydramnios. Browne (1955) believes that oligohydramnios with compression of the foetus is a factor in the development of club foot deformity. For example, Davidson and Ross (1954) described six cases of Potter's syndrome, all of which had club foot. Although mechanical pressure of the uterus may well explain the club foot deformity associated with renal agenesis and oligohydramnios, there are no grounds for believing that the gross deformity of sympodia could be a consequence of these conditions.

Potter (1946) also described for the first time the hypoplasia of the lungs which occurs in renal agenesis. This foetus showed the hypoplasia to a marked degree, the left lung filling only a fraction of the cavity. Again, recent reports on sympodia do not discuss this point, although Jolly and Lamont remark that the lungs in their case 'were poorly expanded'. It is again likely that the examination of most cases of sympodia with this point in view would reveal the abnormality. It is not possible to explain the failure of development of the lungs on

mechanical grounds, as the thoracic cavity was normal in size. The reason for the hypoplasia remains obscure.

The absence of the kidneys explains the large flattened appearance of the adrenal gland found in this case and reported in most cases of sympodia, and also by Potter (1946) in her cases of renal agenesis. The development of the kidneys presumably moulds the adrenals into their characteristic shape in the normal foetus.

The observation that all sympodial monsters have but one umbilical artery is a curious finding. In this case it was the right umbilical artery which persisted, although both Ballantyne (1904) and Kampmeier (1927) found, in their cases, that the artery within the umbilical cord was a persistent vitelline artery.

The sex of this foetus is male, and all collected series show a predominance of this sex. Kampmeier (1927) found 38 males out of a series of 52 sympodial monsters, and Potter (1952), in her series of renal agenesis, found a majority of males, only four out of 26 being female.

Summary

A case of sympodia is described, showing a second degree deformity (Symelia unipus).

The association of this deformity with Potter's syndrome, the typical facies, aplasia of the lungs and renal agenesis, is described.

REFERENCES

Bain, A. D. and Scott, J. S. (1960). Renal Agenesis and severe urinary tract dysplasia. *Brit. med. J.*, 1, 841.
Ballantyne, J. W. (1898). The occurrence of a non-allantoic or vitelline placenta in the human subject. *Trans. Edinb. obstet Soc.*, 23, 54.
—— (1904). *Manual of Antenatal Pathology and Hygiene*, Vol. 2: The Embryo. Green, Edinburgh.
Bartholin, T. (1654). *Historiarum anatomicarum rariorum centuria II. Historia XI.* Hafniae, Copenhagen.
Bearn, J. G. (1960). The sympodial foetus, with a consideration of the causation. *Anat. Rec.*, 136, 107.
Bolk, L. (1899). De Sympodie, een voorbeeld van pathologische segmentaal-anatomie. *Geneesk. Bl.*, 4, 301. (Quoted by Kampmeier.)
Browne, D. (1955). Congenital deformities of mechanical origin. *Arch. Dis. Childh.*, 30, 37.
Davidson, W. M. and Ross, G. I. M. (1954). Bilateral absence of the kidneys and related congenital anomalies. *J. Path. Bact.*, 68, 459.
Dodek, S. M. and Friedman, J. M. (1950). A sirenomelian monster. *J. int. Coll. Surg.*, 14, 226.
Dreyfuss, M. (1928). A case of sympus dipus. *Amer. J. Obstet. Gynec.*, 15, 52.
Förster, A. (1861, 1865). *Die Missbildungen des Menschen, nebst einem Atlas.* Friedrich Manke, Jena.
Foulkes, J. F. and McMurray, J. (1954). A case of sympodia. *J. Obstet. Gynaec. Brit. Emp.*, 61, 827.
Glenister, T. W. (1957). Some history and lore relating to teratogenesis. *Charing Cross Hosp. Gaz.*, 55, 105.
Hendry, D. W. and Kohler, H. G. (1956). Sirenomelia ("Mermaid"). *J. Obstet. Gynaec. Brit. Emp.*, 63, 865.
Hilson, D. (1957). Malformation of ears as sign of malformation of genito-urinary tract. *Brit. med. J.*, 2, 785.
Jolly, H. and Lamont, Edith M. (1958). Sirenomelia: Sympus dipus ("Mermaid"). *Arch. Dis. Childh.*, 33, 226.
Jones, R. L. and Lee, I. N. (1955). A case of symeliac foetus. *Arch. Middlesex Hosp.*, n.s. 5, 188.
Kampmeier, O. F. (1927). On sireniform monsters, with a consideration of the causation and the predominance of the male sex among them. *Anat. Rec.*, 34, 365.
Newbill, H. P. (1941). Sirenomelian monster (sympus). An anatomic presentation. *Amer. J. Dis. Child.*, 62, 1233.
Potter, E. L. (1946). Facial characteristics of infants with bilateral renal agenesis. *Amer. J. Obstet. Gynec.*, 51, 885.
—— (1952). *Pathology of the Fetus and the Newborn.* 1st ed. Year Book Publishers, Chicago.
Resnick, L. (1945). A case of sympus dipus. *J. Obstet. Gynaec. Brit. Emp.*, 52, 515.
Wolff, E. (1936). Les bases de la tératogénèse expérimentale des vertébrés amniotes, d'après les résultats de méthodes directes. *Arch. Anat. (Strasbourg)*, 22, 1.

Addendum

Since this paper was prepared Bain and Scott (1960) have published a series of 50 cases with renal agenesis and other forms of severe urinary tract dysplasia. They report that seven of these had gross defects involving the caudal end of the foetus such as spina bifida or sirenomelia.

ALDRICH'S SYNDROME:
FAMILIAL THROMBOCYTOPENIA, ECZEMA AND INFECTION

BY

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In 1954 Aldrich, Steinberg and Campbell described a family, originally of Dutch extraction, in which the male infants were liable to die at a young age having shown signs of 'draining ears, eczematoid dermatitis and bloody diarrhoea' from the age of a few weeks. They briefly described the clinical features in one child who was a member of this family and who died. They went on to show quite clearly that if the condition which had killed previous male members of the family was the same (as the family itself maintained) then it must have been genetically determined. Since it affected only male members of the family and only some of them, they concluded that the condition must be due to a sex-linked recessive gene which was passed down through the females to the males (in the same way as haemophilia and pseudo-hypertrophic muscular dystrophy). They showed, too, that in the last three generations 16 out of 40 males had been affected and had died within the first 31 months of life. Further evidence of the genetic basis of the condition in Aldrich's family has been produced more recently by Krivit and Good (1959), who report that the two females who appear to carry the gene at the moment, and are reproducing, have produced eight children between them since Aldrich's paper was published. Two of them are girls and are normal, while six of them are boys, three of whom have been affected by the condition. This is what one would expect if it were due to a sex-linked recessive gene. It seems quite definite therefore that in the family described by Aldrich the condition is genetically determined in this way.

Meanwhile Huntley and Dees (1957) have described other white families in which the same condition appears to have been present, and Wolff and Bertucio (1957) have described it in a Negro family. Huntley and Dees contributed considerably towards determining the clinical picture and they described the main features as being 'eczema associated with thrombocytopenic purpura and purulent otitis media'. They described five cases, all of whom died. In only two of these cases, however, was the genetic nature of the condition at all conclusive. These two cases (1 and 2 in their series) were brothers. In their Case 3 no family history was obtainable and in their Case 4 the child was adopted and no family history was available. In Case 5 there was a suggestive but unconvincing family history.

Although Wolff and Bertucio reported their Negro family in 1957, it was only briefly, and further details do not seem to have been published. It is possible therefore to include their family as one in which the abnormal gene is carried, but it is not possible to include the individual cases of the family in this review since full details are not available.

Very recently Mills and Winkelmann (1959) have reported a further three cases in two families. Again all the children were male and there was a strong family history in all of them. Two of them were cousins. All three have died.

To date, therefore, seven* families have been reported, who seem to carry this abnormal gene, and full details are available of 16† cases, some of whom do not have a positive family history but are clinically identical with those who do. All 16 were males and all are dead.

The object of the present communication is to report two cases in an English family which also seems to carry the abnormal gene. One has died and the other is still alive.

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* Aldrich (1); Huntley and Dees (1); Krivit and Good (2); Wolff and Bertucio (1); Mills and Winkelmann (2).

† Aldrich (1); Huntley and Dees (5); Krivit and Good (7); Mills and Winkelmann (3).

Case Reports

Case 1. Patrick G. (54/23984/G) was born on September 30, 1949.

FIRST ADMISSION. On November 2, 1950, at the age of 14 months, he was admitted because of infantile eczema dating from the age of 4 months. This had affected mainly the head, arms, legs and neck. It had also been observed from the age of 4 months that he had a bleeding tendency and that unexplained bleeding had occurred from the nose, ears and gums. This was especially noted by the mother since she had had a brother who was said to have suffered from haemophilia and who died of pneumonia at the age of 1 year, in 1933.

The reason for Patrick's first admission was that some areas of the eczema had started to weep, the serous discharge being bloodstained, and that he had in addition many petechiae and ecchymoses.

The eczema responded well to the dermatologists' treatment but the purpura continued to appear and was shown to be related to a thrombocytopenia which (with the exception of one count) persisted until a splenectomy was performed three years later. The eczema, however, tended to improve and Fig. 1 shows only a quiescent eczema of the ankle, since it was taken primarily to show the purpura. He constantly had similar eczema behind the ears and inconstantly on the face.

FIG. 1.—Case XVII. Patrick G. Shows severe ecchymoses and flexural eczema at ankles.

The only drug which the child had had before admission was phenobarbitone (for the irritation of his eczema), and withdrawal of this led to no improvement in the purpura.

During the first and subsequent admissions numerous references were made in the notes to the ease with which he picked up infections. He was febrile on many occasions, sometimes without any satisfactory explanation being found; on others he had recurrent otitis media, pyodermia, diarrhoea and respiratory infections.

On December 18, 1950 he was discharged home with a quiescent eczema but with an active purpura and thrombocytopenia. He was somewhat anaemic at this stage (Hb 9 g.%) and was given a course of oral iron. His white cell count was 11,000/c.mm. and remained normal throughout except for the polymorph response during the acute infections.

SECOND ADMISSION. He was re-admitted on April 21, aged 19 months, with a recrudescence of his eczema. His platelet count was 178,000/c.mm. (the only normal count obtained before splenectomy), but this rapidly fell again to a low level and the purpura (which had never really been absent) persisted. At this stage a marrow puncture was performed and was reported as showing 'plenty of platelet-forming megakaryocytes'.

On July 11, 1951 he was discharged for the second time, again with quiescent eczema but still thrombocytopenic.

THIRD ADMISSION. He was re-admitted on August 22, 1953, aged 3 years 11 months; the eczema was still quiescent but he had discharging ears, impetigo, bleeding gums and profuse purpura. His platelet count was still low. Once again the skin lesions cleared, and on this occasion he was given A.C.T.H. 25 mg. b.d. for 10 days (the 'ration' which was available at the time). Since the platelet count showed no response further supplies were not requested.

In view of the fact that this child was known to have had thrombocytopenia of severe degree for over three years without remission (other than for one count), it was felt that splenectomy was indicated and this was performed on December 7, 1953 (Mr. F. J. P. O'Gorman). There was an immediate rise in the platelet count, which at one time went to over 600,000/c.mm. and then stabilized at a normal level and remained normal till (at least) four days before he died. In association with this there was a complete disappearance of his purpura and bleeding tendency until the final illness. On January 14, 1954, he was discharged for the third time.

FOURTH ADMISSION. On January 26, 1954, 12 days after his third discharge, he was admitted as an emergency, having been gravely ill for 24 hours. He was unconscious with a low B.P. (55/0) and no fever. In spite of this the clinical condition seemed to be compatible with a septicaemia and he was treated accordingly. He proceeded to develop a pneumococcal meningitis and responded well to treatment. Once this was stopped he relapsed, and this time the meningitis was said to be

staphylococcal in origin. This also
responded satisfactorily to treatment.

He was discharged home for the fourth
time on April 4, 1954. His platelet count
was still normal and it had been established
that he did not have agammaglobulinaemia.

FIFTH ADMISSION. This was on July 5,
1954 for dental extractions which proceeded
without incident.

When seen in the out-patient department
on October 1, 1954, he was found to be well
and without purpura. His platelet count
was 228,000/c.mm.

SIXTH ADMISSION. He was admitted as
an emergency on October 5, 1954, aged
5 years, having been ill for only 12 hours
with symptoms similar to the illness of his
fourth admission, but his condition had
deteriorated very rapidly and on admission
he was moribund. At autopsy he had
bilateral adrenal haemorrhage of the kind found in the
Waterhouse-Friderichsen syndrome. No proof of a
septicaemia was obtained on this occasion.

SUMMARY. This boy showed signs of infantile eczema
and purpura from the age of 4 months. A maternal
uncle had suffered from a bleeding tendency and had
died of pneumonia at the age of 1 year. The present
patient's eczema persisted but tended to improve as the
years went by; his purpura was associated with thrombo-
cytopenia and they both persisted until splenectomy was
performed at the age of 4 years 2 months. Thereafter
the platelets rose to a normal level and the bleeding
tendency disappeared. He had always tended to show
signs of minor infections but some weeks after splenec-
tomy he developed pneumococcal septicaemia with
meningitis and then relapsed with a staphylococcal
meningitis. He responded well to treatment. At the
age of 5 years, 10 months after splenectomy, he still had
a normal platelet count, but five days later he was
admitted moribund having been ill for only 12 hours
(again with symptoms suggestive of septicaemia) and he
died shortly afterwards. Autopsy showed massive
bilateral adrenal haemorrhage.

Case 2. Christopher G., brother of Patrick, was born
on August 31, 1957.

Between the births of these two children (see the family
tree in Fig. 2) a boy and a girl had been born, both of
whom are perfectly healthy and show none of the
manifestations of the condition.

Christopher was also thought to be normal until he was
3 months old when the family doctor (Dr. E. D. Forster)
noted that he had petechiae on the neck (Fig. 3). At
4 months he was admitted for investigation and by that
time he had some eczema behind the left ear although
his eczema never became so severe as Patrick's. On
admission he had a definite thrombocytopenia as a cause
of his purpura and his ability to pick up infection was

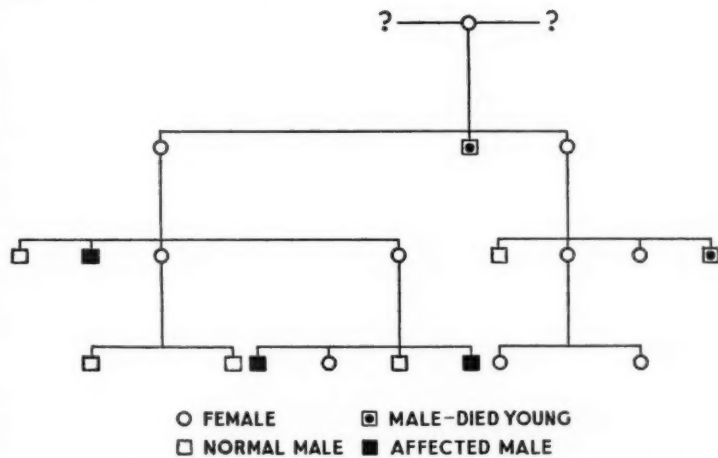FIG. 2.—Shows G. family history as far as it can be constructed at the moment.

also demonstrated during his stay in hospital since he
developed furunculosis, pyuria and frequent bronchitis
but never otitis media. It was established that he also
did not have agammaglobulinaemia and his white count
throughout was normal.

FIG. 3.—Case XVIII. Christopher G. Shows purpura on neck and
minimal changes of eczema behind ear.

Marrow puncture was performed and reported as showing 'adequate megakaryocytes present but reduced platelet formation'.

Attempts to stimulate platelet formation by means of A.C.T.H. and prednisolone were only temporarily successful. In view of our experience with Patrick after splenectomy it was decided that this operation was not indicated in Christopher's case so he was discharged home, still with a low platelet count.

He has remained well since, apart from frequent respiratory infections during the winter months, and he is now a well developed toddler who still gets occasional crops of petechiae but whose eczema is well healed.

SUMMARY. Christopher G., brother of Patrick, had petechiae at 3 months and slight eczema at 4 months. He has always been liable to pick up infections. He has thrombocytopenia which only temporarily responds to

A.C.T.H. and steroids. He does not have agamma-globulinaemia. He is now (April, 1960) a healthy child with occasional petechiae and recurrent respiratory infections.

Charts showing the changes in the platelet counts in response to A.C.T.H., prednisolone and splenectomy in the two brothers are shown in Figs. 4 and 5.

Table 1 shows the main features in the 18 cases described so far. All the cases showed eczema but this was of variable severity.

All the cases showed purpura and, except for Case VIII, they all showed persistent thrombocytopenia, too. In Case VIII only one count was done and it was normal, but this may well have been a temporary spontaneous rise such as occurred in

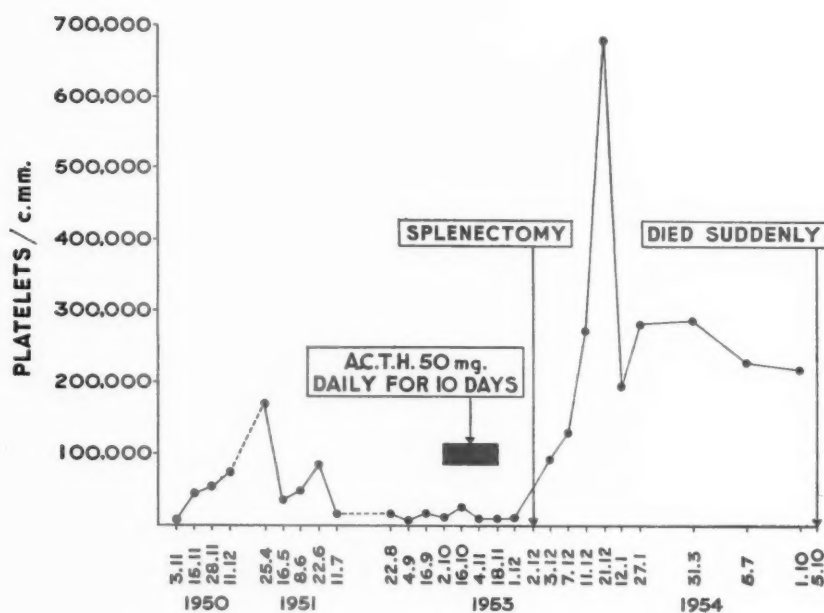

FIG. 4.—Shows platelet level over four years of Patrick G. with absence of response to a small dose of A.C.T.H. and dramatic response to splenectomy which was maintained until at least four days before his sudden death.

FIG. 5.—Shows platelet level over six months of Christopher G. There is absence of response to prednisolone (P) (158 mg. over 46 days) and only partial response to A.C.T.H.
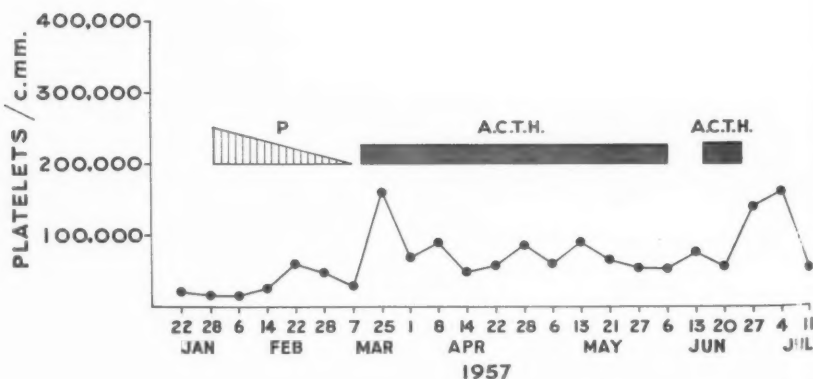
TABLE 1

ANALYSIS OF CASES REPORTED IN THE LITERATURE

	1	II	III	4	5	6	VII	VIII	9	X	11	12	XIII	XIV	XV	XVI	XVII	XVIII
Age at onset	1 m.	3 m.	5 d.	2 w.	2 w.	3 m.	5 m.	3 d.	1 d.	3 w.	11 d.	6 d.	9 d.	Birth	2 w.	2 w.	4 m.	3 m.
Age at death	11 m.	22 m.	2 yr.	14 m.	2 yr.	7 yr.	3 yr.	2 yr.	8 m.	1 yr.	20 m.	2 yr.	23 m.	15 m.	5 m.	3 yr.	5 yr.	A
Clinical features:																		
Purpura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thrombocytopenia	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+
Eczema	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Infections:																		
Pyodermia	+	+						+			+	+	+		+	+	+	
Pneumonia								+			+	+		+	+	+		
Otitis media	+	+	+	+	+	+	+		+	+	+		+			+	+	
Meningitis		+	+														+	
Septicaemia	+															+	+	
Pyrexia	+						+		+		+						+	+
Treatment of thrombo- cytopenia:																		
A.C.T.H.			+		+					+							+	+
Steroids			+			+				+		+			+	+	+	+
Splenectomy	+	+	+		+	+				+					+		+	+
Mode of death	H	I	I	I	H	I	H	H	I	H	I	I	I	I	I	I	H	A

Cases with strong family histories in Roman numerals, those without in Arabic. Case 1 is Aldrich's original case; Case XIII Krivit and Good's follow-up of Aldrich's family; Cases II-6 are those of Huntley and Dees; Cases VII-XIII are those of Krivit and Good; Cases XIV-XVI are those of Mills and Winklemann; Cases XVII and XVIII are described in the present communication. We have not been able to trace details of Wolf and Bertucio's family.
H = death from haemorrhage; I = death fom infection; A = alive.

Patrick. The thrombocytopenia is very important diagnostically since it is the only positive laboratory finding which occurs as an essential part of the syndrome.

Infection of one kind or another occurred in all the cases and was responsible for at least 11 of the deaths which have occurred. It should be noted how frequently otitis media has been present but this is almost certainly a reflection of these children's poor resistance to infection rather than of any specific defect in their middle ears.

Since the family history is so important cases with a strongly suggestive family history have been numbered in Table 1 differently from those without. The two cases recorded in the present communication, apart from being brothers, had an uncle who died in infancy apparently from the same condition. The mother of that child, i.e. the grandmother of our two cases, is alive and has given a detailed account of him. He died of pneumonia at the age of 1 year (1933) but before then she was told by the family doctor that he suffered from 'haemophilia'. This was because he bled very easily and he frequently came out in 'large bruises just like Patrick's'. The rest of the family history (Fig. 2) shows that two other male children died young but there was no evidence to show that they had either a haemorrhagic tendency or eczema.

Unfortunately no further family history is available since the grandmother, Mrs. T., went to New Zealand as a child (her parents having died) and

she has completely lost touch with her mother's family. She thinks that her mother had some sisters but does not know where their descendants might be.

Discussion

Although the various clinical aspects of this condition occur separately, and some of them quite commonly, it is unusual for them all to occur in one individual and certainly in members of the same family. Long before we read the original papers on this subject we had decided that this was an unusual family. There are four main features of the condition and they will be discussed separately. In each case the patient has been a male and the symptoms have appeared within the first six months of life.

Thrombocytopenia. This has led to the most common symptom, namely, bleeding. This includes purpura, epistaxis, 'bloody diarrhoea', haematuria, bleeding gums and cerebral haemorrhage, in fact any of the manifestations of bleeding which occur with thrombocytopenia at any age. Six of the 17 deaths appear to have been due to haemorrhage but in two of these (including Patrick) the haemorrhage was into the adrenals and may have been secondary to a fulminating septicaemia.

The cause of the thrombocytopenia in these cases is no clearer than it usually is in 'essential thrombocytopenia'. There are certainly adequate numbers

of megakaryocytes present in the bone marrow so that either they do not produce enough platelets or the platelets they do produce have a shorter life than normal. The latter could result either from a defect in the platelets themselves or from the presence of a platelet-agglutinating antibody. No evidence of such an antibody was found in two of Krivit and Good's patients and, in any case, if the condition is genetically determined some congenital defect in the production or formation of platelets seems more likely than excessive destruction of normal platelets.

We do not even know yet whether the condition is congenital or not. Since the only part of the syndrome which is likely to be present at birth is the thrombocytopenia, it will be necessary to do platelet counts on the cord blood of future infants born to the affected families. Although Case XIV is shown as having symptoms from birth, this information was based on the mother's history and not on observation.

Eczema. This appears to be identical with the usual infantile eczema except that in certain cases bleeding has occurred into the eczematous areas. The severity of the skin lesions has varied from time to time even in one patient and has varied considerably from one patient to another. Even in our two brothers the eczema was more severe in Patrick than in Christopher. Mills and Winkelmann (1959) point out that the eczema is the least specific of the clinical features in these children and we agree with this.

Liability to Infection. This is the most difficult part of the syndrome to define, since, of course, most infants in the first year of life are liable to pick up infections. The infections which these affected babies have are of the usual variety and include pyodermia and respiratory infections in addition to the otitis media which has occurred in nearly every case. It is characteristic of these children, too, that they run fevers for which no satisfactory explanation can be found. It can be seen from Table 1 that a considerable number die from infections in spite of antibiotic therapy. This has occurred in those on whom splenectomy has not been performed (Cases 4, 9, 11, 12, XIII, XIV, XVI) as well as in those whose spleens have been removed (Cases II, III, 6, XV, ?XVII). It is well known that King and Shumacker (1952) and Smith, Schulman, Stern and Erlandson (1956) have suggested that splenectomy in young children may be followed by death from fulminating infection. In Smith's series this occurred in 28% of his 50 patients who had had splenec-

tomy performed under the age of 2 years for any reason at all, including trauma. In spite of the fact that there is evidence against this contention (Gofstein and Gellis, 1956) as well as in favour of it, we felt that splenectomy should not be undertaken in Christopher. Krivit and Good (1959) are also of the opinion that there is an increased liability to severe infection after splenectomy. They were, however, unable to find any alteration in known immune mechanisms in two of their cases on whom intensive investigations were performed. In all cases on whom gamma globulin estimations have been performed it has been found to be present in normal amounts, and the white cell counts have also been normal. There is therefore no explanation for the liability of these infants to infection.

Family History. There have now been reported eight families showing both the clinical features of Aldrich's syndrome and the family history, which is strongly suggestive of its genetic basis. In the other cases all the affected children have been males but there has been no clear-cut history of the condition occurring in other male relatives. Since it was the genetic basis of the condition which Aldrich laid down, it seems wise to limit the syndrome bearing his name to those cases in which there seems to be a reasonable certainty that, in addition to occurring in males, it has been genetically determined by a sex-linked recessive gene.

It is, of course, often found that conditions such as infantile eczema are familial, and they are often thought to indicate a familial tendency to allergy. Thrombocytopenia, too, is often thought to have an 'allergic' basis and it is not surprising that American writers have concentrated on the possibility of one allergic factor being responsible for both parts of the syndrome. Although in certain cases true allergic responses have been obtained, there does not appear to be any clear-cut evidence that the symptoms are due to any specific antigen-antibody reaction. Following the usual British practice at the present time, skin reactions, etc. were not performed on either of our two patients so that information on this point is not available.

As with all familial conditions, the parents and relatives all worry about what is likely to happen to future children who are born into the family. Once the genetic basis becomes clear, as we believe it has in this syndrome, it becomes easier for the physician to give the family the facts, as far as they are known, and this can reassure the relatives considerably even though they realize that half of the further male children may be affected.

It is customary, whenever someone is writing

about a relatively new syndrome, to say that cases are likely to be found more frequently in the future once people start looking for them. This is not likely to happen to any great extent in Aldrich's syndrome since, although other families will probably be described, it is unlikely that they are at all numerous. The importance of the syndrome lies more in the fact that it is a newly recognized disease process due to a sex-linked gene, and the components of the syndrome all occur fairly commonly as separate entities.

Summary

A further family is reported which seems to suffer from Aldrich's syndrome.

The syndrome consists of thrombocytopenic purpura, eczema and infection occurring in male infants and leading eventually to death from haemorrhage or infection. It is genetically determined and is due to a sex-linked recessive gene.

It has not yet been shown whether or not the condition is congenital.

REFERENCES

Aldrich, R. A., Steinberg, A. G. and Campbell, D. C. (1954). Pedigree demonstrating a sex-linked recessive condition characterised by draining ears, eczematoid dermatitis and bloody diarrhoea. *Pediatrics*, 13, 133.

Gofstein, R. and Gellis, S. S. (1956). Splenectomy in infancy and childhood. *A.M.A. J. Dis. Child.*, 91, 566.

Huntley, E. C. and Dees, S. C. (1957). Eczema associated with thrombocytopenic purpura and purulent otitis media. *Pediatrics*, 19, 351.

King, H. and Shumacker, H. G. (1952). Splenic studies 1. Susceptibility to infection after splenectomy performed in infancy. *Ann. Surg.*, 136, 239.

Krivit, W. and Good, R. A. (1959). Aldrich's syndrome (thrombocytopenia, eczema and infection in infants). *A.M.A. J. Dis. Child.*, 97, 137.

Mills, S. D. and Winkelmann, R. K. (1959). Eczema, thrombocytopenic purpura and recurring infections. *A.M.A. Arch. Derm.*, 79, 466.

Smith, C. H., Schulman, I., Stern, G. and Erlandson, M. (1956). Benefits and hazards of splenectomy in severe chronic anemias in children. *Proceedings of the 8th International Congress of Paediatrics, Copenhagen, Abstracts*, p. 146.

Wolff, J. A. and Bertucio, M. (1957). A sex-linked genetic syndrome in a Negro family manifested by thrombocytopenia, eczema, bloody diarrhea, recurrent infection, anemia and epistaxis. *A.M.A. J. Dis. Child.*, 93, 74.

EFFECT OF CORTICOTROPHIN
ON HYPOTHALAMIC SYNDROME IN CHILDREN

BY

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Bauer (1954), in reviewing 60 cases of hypothalamic syndrome reported at all ages in the literature, named the principal signs in descending order of frequency as precocious puberty, hypogonadism, diabetes insipidus, psychic disturbances, somnolence, obesity, thermodysregulation, emaciation, convulsions, sphincter loss, bulimia, anorexia and dyshydrosis. Some of the above signs are clearly due to abnormal secretion by the pituitary gland, and those specifically resulting from a deficiency of adrenocorticotrophic hormone might be expected to respond to replacement therapy since the value of corticotrophin (or of cortisone) is well established in the prevention and treatment of hypopituitary coma (Caughey, 1958). The pituitary gland is under the control of the hypothalamus and it is not clear whether certain signs are due purely to hormone deficiency or to direct interference with the hypothalamic vegetative centres; this applies to disturbance of appetite and body weight, mental alertness and body temperature. Damage to hypothalamic centres by an astrocytoma causes emaciation and increased appetite in the syndrome described by Russell (Russell, 1957; Kagan, 1958); these symptoms do not respond to corticotrophin in spite of other evidence of depression of pituitary function. Damage to the vegetative centres probably also explains the failure to respond to corticotrophin or cortisone in some cases of collapse following operation in the hypothalamic region (Northfield, 1955).

We now report four cases of hypothalamic syndrome in whom a stuporose state responded well to treatment with corticotrophin, which suggests that the underlying cause might be anterior pituitary deficiency rather than damage to the vegetative centres. Anorexia and wasting, which accompanied the stuporose state in two of the cases, also responded to corticotrophin. A space-occupying lesion at the base of the brain was accompanied in all these cases by an endocrine disturbance, in three cases by diabetes insipidus and in one by precocious puberty.

The four cases came under the care of Mr. Wylie McKissock at The Hospital for Sick Children, Great Ormond Street.

Case Reports

Case 1 (R.S.). At the age of 9½ years this boy had a convulsion with residual weakness of the left arm. Two and a half years later he developed diabetes insipidus. He was admitted to The Hospital for Sick Children, Great Ormond Street. After air studies had been carried out it was concluded that there were intracranial lesions in the right frontal and pineal regions. A large port-wine naevus over the right forehead indicated that cerebral angiomata were probably present. During the next year the patient became progressively listless. Papilloedema developed and a further ventriculogram carried out in Sweden confirmed multiple intracranial lesions (Professor Olivecrona). The basal metabolic rate was found to be minus 34 per cent. Thyroid extract effected an improvement. Eight months later he was readmitted to The Hospital for Sick Children, Great Ormond Street, having been doubly incontinent for a month. His fluid intake, previously high, was estimated to have gone down to approximately one litre daily and he was refusing food. He was found to be in a grossly wasted, stuporose and apathetic state. He was hypothermic (oral temperature 95° F. (35° C.)) and the blood pressure was 60/40 mm. Hg. The urinary 17-ketosteroid excretion was 1·2 mg./24 hours and the 17-hydroxysteroids were 2·7 mg./24 hours.* The blood cholesterol was 98 mg. per 100 ml. A glucose tolerance test gave the following figures: fasting 82 mg., and then at 30-minute intervals after an initial 50 g. of oral glucose, 91, 132, 176, 252 and 169 mg. per 100 ml. Plasma

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* In our laboratory the normal range for 17-ketosteroids for children of 9 to 12 years is 1·1–9·5 mg./24 hours, mean 3·8 mg./24 hours; and for 17-hydroxysteroids, 1·0–8·2 mg./24 hours; mean 3·8 mg./24 hours.

electrolyte values were all increased; the plasma sodium was 156 mEq./l., the plasma potassium 5·9 mEq./l. and the plasma urea 137 mg. per 100 ml.

PROGRESS AFTER CORTICOTROPHIN. Replacement therapy was started with corticotrophin 20 mg. b.d. The fluid intake was raised to 3½ l. daily to counteract hyperelectrolytaemia, but pitressin was not given at this stage. The calorie intake was kept at approximately 2,000 calories, using a fortified dried milk preparation with added vitamins (Complan). During the next two days the patient became more alert, his oral temperature rose to normal and the blood pressure increased to 130/70 mm. Hg. There was a good eosinophil response to the first dose of corticotrophin with a fall from 238 to 128 per c.mm. in four hours and subsequently to 40 per c.mm. The urinary 17-ketosteroids rose steadily to 9·3 mg./24 hours, and the 17-hydroxysteroids to 25·4 mg./24 hours. Corticotrophin was then cut down by stages to 5 mg. daily and on this dosage the patient's condition remained greatly improved. The output of urine was now 2-3 l. daily. The hyperelectrolytaemia remained unchanged. The fluid intake was therefore increased to 5 l. daily and pitressin was started in a dosage of 1 unit daily. Four days later the patient rapidly became disorientated and then comatose. It was thought that this was probably due to overhydration. Intravenous saline was given, followed, as he improved, by sodium chloride orally and D.O.C.A. 5 mg. daily by injection. Subsequently he began to lose salt through the kidney, and sodium chloride by mouth and D.O.C.A. were relatively ineffective in maintaining the plasma sodium chloride level in equilibrium. It was thought that a cerebral salt-wasting syndrome had developed, though the possibility of salt loss induced by over-hydration could not be excluded. Two months later a ventriculogram was done with a view to a subsequent brain biopsy. Two hours after ventriculography the patient became profoundly unconscious and there was an abrupt fall in the excretion of sodium. This collapse was presumably due to damage to the vegetative centres. He died in coma two weeks later.

At autopsy (Dr. Martin Bodian) the diagnosis of cerebral angiomata was confirmed. The hypothalamus was involved by an angioma but this was not invading the pituitary gland.

COMMENT. In this boy with a cerebral angioma involving the hypothalamus, improvement in alertness, weight and appetite showed that corticotrophin had been of benefit. Long-standing diabetes insipidus later became complicated by a salt-losing syndrome and further damage to the vegetative centres led to coma and death.

Case 2 (M.H.). This girl, aged 10½ years, had a year's history of lethargy, poor appetite and loss of weight, with headaches and vomiting for six months. The child was admitted to The Hospital for Sick Children, Great Ormond Street, where ventriculography showed a suprasellar space-occupying lesion largely blocking the third ventricle. She was transferred to the National Hospital for Nervous Diseases, Queen's Square, where an inoperable suprasellar tumour was found and was implanted with radioactive gold seeds. Post-operatively she developed a right hemiparesis. She became very drowsy and the blood pressure fell to 70/50 mm. Hg. Next day her condition was still stuporose and the oral temperature was 94° F. (34·4° C.). At this time the plasma sodium was 131 mEq./l., potassium 5·1 mEq./l. and urea 75 mg./100 ml. Urinary steroid levels were low; 17-ketosteroid excretion was 0·7 mg./24 hours and 17-hydroxysteroids were less than 1·0 mg./24 hours. The plasma cholesterol was 276 mg. per 100 ml.

PROGRESS AFTER CORTICOTROPHIN. Therapy was commenced with 10 mg. b.d. of corticotrophin, subsequent to which the temperature rose progressively to 98° F. (36·7° C.) and she became much brighter. Right hemiparesis and dysphagia remained. A month after the operation marked thirst was first noticed and found to be due to diabetes insipidus. Pitressin was not given at this stage. Two weeks later corticotrophin was reduced to 10 mg. daily and she was sent away for one month's convalescence. On her return she was found to be obese (weight gain 5·9 kg.) and was noticed to show excessive hunger and unpredictable changes of mood. The plasma electrolyte levels were within normal limits. The urinary 17-ketosteroid excretion was 10·8 mg./24 hours. Corticotrophin was discontinued, but during the subsequent week the patient again developed anorexia, apathy and a tendency to sleep during the day. Corticotrophin was recommenced in a dosage of 10 mg. every other day with good effect. She went out of hospital well stabilized on this dose and also on pitressin snuff 30 units daily. After a further three months corticotrophin was gradually reduced and she was doing well on pitressin alone six months later.

COMMENT. In this case of hypothalamic syndrome due to suprasellar tumour, lethargy and hypothermia responded well to corticotrophin. The patient's requirements fell rapidly but attempts to withdraw the drug after three weeks were unsuccessful, though treatment was successfully discontinued three months later. Diabetes insipidus developed post-operatively. This was the only case in the series in which urinary steroid excretion was below normal before treatment.

Case 3 (P.H.). This girl, aged 10 years, had a history of excessive thirst and polyuria for three years. Deterioration of vision had been present for two years, culminating in complete blindness in the right eye one month before admission. Headaches, vomiting and somnolence were recent features. On admission to The Hospital for Sick Children she was drowsy but cooperative. The blood pressure was 95/60 mm. Hg. The urinary specific gravity never rose above 1·003 and a diagnosis of diabetes insipidus was made. Ventriculography showed a space-occupying lesion in the pituitary-hypothalamic region. Craniotomy revealed a dark red

mass which appeared to be welling from the pituitary fossa. Removal was impossible. It had the appearance of a teratoma and this was confirmed histologically. After the operation she remained drowsy, waking only to be fed. Body temperature was normal. The plasma sodium was 134 mEq./l. and plasma potassium 4·4 mEq./l. The urinary 17-ketosteroids were 3·5 mg./24 hours and the 17-hydroxysteroids 2·2 mg./24 hours.

PROGRESS AFTER CORTICOTROPHIN. Corticotrophin, 20 mg. b.d., was given in view of the drowsiness. Within 48 hours she became much more alert with an increased appetite and by the fourth day she wanted to get out of bed. The urinary 17-ketosteroids rose to 17·9 mg./24 hours and the 17-hydroxysteroids to 41·7 mg./24 hours. Corticotrophin was gradually withdrawn after 10 days, and five days after the last dose she was transferred to another hospital for radiotherapy. The drowsiness returned rapidly but again responded promptly to corticotrophin, which was discontinued after three weeks, this time without any recurrence of symptoms. Nine months later she remained well.

Before craniotomy the average daily urinary output in this patient was 1·4 l., rising to 2·2 l. during the five days following operation; after five days on cortico-trophin it reached 9·7 l./24 hours, whereupon cortico-trophin was withdrawn. No pitressin was being given at this time.

COMMENT. As in the previous case corticotrophin was principally of benefit post-operatively in im-proving the alertness of a patient with suprasellar tumour and diabetes insipidus. A relapse occurred during radiotherapy but a second course was needed for only three weeks and the patient was well apart from diabetes insipidus nine months later.

Case 4 (D.R.). The patient was a boy aged 9 years. At the age of 8 years pubic hair and enlargement of the penis were noticed. Six months later vomiting began. Five weeks before admission he had two major convul-sions and thereafter developed headaches, anorexia, lassitude and a squint. On admission he answered questions readily, though he was otherwise lethargic and content to lie in bed all day. He was emaciated (weight 48 lb. (21·8 kg.)) (Fig. 1). The penis and testes were of adult proportions. The temperature was normal and the blood pressure 140/90 mm. Hg. The plasma sodium was 132 mEq./l. and the plasma potassium 5·1 mEq./l. The urinary 17-ketosteroids were 2·6 mg./24 hours and the 17-hydroxysteroids 5·9 mg./24 hours. A glucose tolerance test was normal with a fasting level of 97 mg. and at 30-min. intervals after 25 g. of glucose 97, 156, 135, 97, 103 and 97 mg. per 100 ml. Ventriculography showed space-occupying lesions in the left subfrontal and suprasellar regions; there was also internal hydro-cephalus and the presence of a third lesion in the posterior fossa was suspected. Craniotomy was not undertaken because of multiple lesions. During the next two weeks the patient remained lethargic and his emaciation continued in spite of adequate fluid and calorie intake with 'complan' via a nasal catheter.

FIG. 1.—Case 4. On admission. Note gross emaciation and sexual precocity.

PROGRESS AFTER CORTICOTROPHIN. Corticotrophin 20 mg. daily was then given. Six days later he was less lethargic, gaining weight and feeding himself. The

FIG. 2.—Case 4. Shows response of emaciation to corticotrophin.

urinary 17-ketosteroids were 6·1 mg./24 hours and the 17-hydroxysteroids 6·2 mg./24 hours. His weight increased slowly to 61 lb. (27·7 kg.) a month later. He was by then fully alert but not euphoric. He was transferred to another hospital for deep x-ray therapy after which corticotrophin was gradually withdrawn. Three months later his clinical condition remained good and he has continued to improve (Fig. 2).

COMMENT. Here, as in Case 1, lethargy and emaciation were associated with a suprasellar lesion as part of multiple inoperable intracranial lesions. A rapid response occurred to corticotrophin, which was later withdrawn successfully after radiotherapy. Isosexual precocity was also a feature.

Discussion

The fact that the administration of corticotrophin coincided with correction of stupor and improvement in the general condition of all four patients suggests that there was an initial depression of pituitary adrenocorticotrophin secretion for which corticotrophin acted as a replacement. However, laboratory investigations provided little confirmatory evidence of adrenocortical deficiency. Glucose tolerance tests in two of the patients did not show the typical change of hypoglycaemia over-responsiveness. Insulin tolerance tests were not performed. The eosinophil response after corticotrophin was measured in Case 1; this was normal, whereas in hypopituitarism a delayed or diminished depression of the eosinophils from secondary adrenocortical failure may occur, depending upon the duration of the pituitary failure (Nabarro, 1957). In our cases the plasma sodium and potassium levels did not show changes typical of adrenocortical failure. There was no delayed increase in steroid excretion after corticotrophin was administered. Two cases (1 and 3) showed a marked diuresis after the administration of corticotrophin, but this is not strictly evidence of initial depression of adrenocorticotrophic hormone secretion since a rise in solute excretion may occur consequent upon an increase in appetite. On a fixed dietary intake corticotrophin will not influence urinary volume in cases of anterior and posterior pituitary deficiency (Leaf, Manby, Rasmussen and Marasco, 1952). The overhydration which occurred in Case 1 was due to excess intake of water and pitressin and not to lack of corticosteroids since at that time corticotrophin had already been administered and steroid excretion was well within the normal range. The special investigations therefore showed no major deficiency in those aspects of the pituitary-adrenocortical mechanism which could be investigated.

Cases of post-operative coma due to tumours in and around the pituitary gland have previously been reported to respond to steroid replacement; in contrast to our cases, these usually showed evidence of long-standing pituitary deficiency and required permanent substitution therapy. In our three cases, who survived, corticotrophin was withdrawn successfully. If, as seems likely, there was no permanent or severe damage to the hypothalamic anterior pituitary system in our cases, the response to corticotrophin must be explained on a different basis. Two possibilities might account for the beneficial effect. First, the improvement may have been due to excessive secretion of corticosteroids which the corticotrophin stimulated. Corticosteroids improve the appetite and alertness in normal subjects. An alternative explanation is that there was a temporary depression of adrenocorticotrophic hormone, not shown in our tests, and that this was reversed by the general improvement which followed hormonal and surgical treatment. Full assessment of anterior pituitary activity was handicapped in two ways; first, by the ill state of the children which precluded full endocrine investigations, and second, by the fact that they had not reached the age of puberty; after puberty the recognition of hypopituitarism may be made more easy by such signs as hypogonadism, loss of pubic and axillary hair and low steroid excretion.

Whatever the explanation, the amelioration in the stupor and general condition of the four children was striking and it appears advisable to administer corticotrophin to children with lesions in the hypothalamic-pituitary region before surgery is undertaken. All our cases had an associated endocrine abnormality, such as diabetes insipidus or precocious puberty, though in one child the endocrine defect did not appear until post-operatively; this is in contrast to one case of suprasellar tumour we have seen recently in a boy of 9, who showed no associated endocrine defect and in whom the wasting and stupor did not respond to corticotrophin.

Summary

The response to treatment with corticotrophin is described in four cases of hypothalamic syndrome, i.e. children with space-occupying lesions at the base of the brain associated with endocrine disturbances, stupor and wasting.

The difficulties of diagnosing anterior pituitary deficiency in the pre-pubertal child are discussed and it is suggested that all children with lesions in the region of the hypothalamus and pituitary gland should be given corticotrophin (or cortisone) before surgical intervention.

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REFERENCES

Bauer, H. G. (1954). Endocrine and other clinical manifestations of hypothalamic disease; survey of 60 cases with autopsies. *J. clin. Endrocr.*, 14, 13.
Caughey, J. E. (1958). In *Modern Trends in Endocrinology*, p. 132. Edited by H. Gardiner-Hill. Butterworth, London.
Harris, G. W. (1955). *Neural Control of the Pituitary Gland.* Edward Arnold, London.
Kagan, H. (1958). Anorexia and severe inanition associated with a tumour involving the hypothalamus. *Arch. Dis. Childh.*, 33, 257.
Leaf, A., Mamby, A. R., Rasmussen, H. and Marasco, J. P. (1952). Some hormonal aspects of water excretion in man. *J. clin. Invest.*, 31, 914.
Nabarro, J. D. N. (1957). The diagnosis of adrenal critical dysfunction. *Brit. med. J.*, 2, 1018.
Northfield, D. W. C. (1955). Discussion on pituitary syndromes. *Proc. roy. Soc. Med.*, 48, 879.
Russell, A. (1957). A diencephalic syndrome of hyperkinetic emaciation typically linked to predominant elation in infancy and early childhood. *Excerpta med. (Amst.)*, *Sect. VIII*, 10, Congress Issue, p. 111. 6th International Congress of Neurology, Brussels.

SERUM PROTEIN PATTERN IN INFANTS WITH NUTRITIONAL DISORDERS

BY

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Paper electrophoresis for studying the serum protein pattern is of particular value in infancy because of the small volume of blood required. Despite improved methods of diagnosis and increased knowledge of the aetiology of wasting disorders in infancy, some cases of failure to thrive still present diagnostic difficulties. Cases in which diarrhoea, respiratory infection and wasting are associated are common, and in many such cases investigation of pancreatic function shows this to be depressed. After suitable treatment, which may include pancreatin, these infants are found on reinvestigation to have normal pancreatic function. Fibrocystic disease of the pancreas can then be excluded.

The present investigation was undertaken to find out if the serum protein pattern would be of any diagnostic value in wasted infants in whom the exact diagnosis was in doubt.

Methods and Material

Electrophoretic separation was carried out in a vertical tank of the type described by Flynn and De Mayo (1951), using a barbiturate buffer of pH 8·6. The samples of 0·05 ml. serum were run for 16 hours at a current of 0·25 mA per centimetre width of paper. Whatman paper No. 31M extra thick was used throughout. After drying, the strips were stained for 16 hours in 0·01% bromophenol blue according to the method of Block, Durrum and Zweig (1955). The individual fractions were estimated by the method of Levin and Overholzer (1953), which involves the estimation of the nitrogen in each fraction after the strips have been divided. A correction for the nitrogen in the paper was made by estimating the nitrogen in a measured length of paper from protein-free areas at the ends of the strips. The sum of the individual fractions was checked with the total serum protein as determined by the micro Kjeldahl method.

The sera of 67 infants were examined. Twenty were normal infants known to be taking a satisfactory diet; they were free from infection and of normal weight. These infants served as controls and ranged in age from 7 weeks to 10 months. The other 47 infants were divided into four groups according to the main presenting symptom. Sixteen were wasted infants whose failure to thrive was attributed to underfeeding. Infection was not a complicating factor in these cases which were usually the result of maternal ignorance, though in a few cases actual neglect was involved. The second group consisted of nine infants with acute diarrhoea. The sera of these cases was examined as soon as their clinical condition permitted, in all cases after adequate re-hydration. Only severe cases with marked loss of weight were included. Thirteen were cases of chronic or recurrent diarrhoea. Most of these had a history of repeated bouts of diarrhoea over the previous few months. No single attack was usually of sufficient severity to warrant hospitalization, but advice was eventually sought on account of the frequent recurrence of symptoms and the failure to gain weight, or actual loss of weight, over a long period of time. The remaining nine infants suffered from chronic or repeated respiratory infections of varying severity. The attacks were usually accompanied by pyrexia and were often of sufficient severity to require treatment with antibiotics. In general this group of infants had maintained their weight somewhat better than the other groups and their average age was greater.

An attempt to assess the pancreatic function in these infants was also made by means of amino-acid absorption curves after a gelatin meal and when possible by duodenal intubation and measurement of the tryptic activity of the duodenal contents (Bate and James, 1956; unpublished data). The amino-acid curves were performed according to the method of West, Wilson and Eyles (1946). The criterion of normality was a rise in blood amino nitrogen to a level of at least 3 mg. per 100 ml. above fasting values at some time during the first one and a quarter hours after the gelatin was given. This increase in amino nitrogen was sustained for two and a half hours after the feed in normal infants, after which the level fell towards the fasting values.

Results

The serum protein patterns in normal infants and in those with chronic nutritional disturbances are

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TABLE 1

SERUM PROTEIN LEVELS IN NORMAL INFANTS AND IN INFANTS WITH NUTRITIONAL DISTURBANCES

| | Total (g.%) | Albumin (g.%) | Globulins | | | | Average Age | Cases |
			α_1 (g.%)	α_2 (g.%)	β (g.%)	γ (g.%)		
Normals	6·392	3·825	0·327	0·837	0·775	0·617	7 mth.	20
S.D.	0·66	0·41	0·06	0·10	0·11	0·15		
Undernutrition	6·171	3·125*	0·477†	0·902	0·865	0·802§	7 mth.	16
S.D.	0·71	0·45	0·28	0·30	0·19	0·42		
Acute diarrhoea ..	5·669	3·016*	0·378	0·872	0·767	0·634	7 mth.	9
S.D.	0·69	0·49	0·13	0·15	0·25	0·12		
Chronic diarrhoea ..	5·980	2·955*	0·504*	0·980§	0·807	0·732	6 mth.	13
S.D.	0·63	0·53	0·17	0·25	0·18	0·27		
Respiratory infections ..	6·308	3·357‡	0·394	0·970	0·778	0·806	13 mth.	9
S.D.	0·73	0·46	0·13	0·18	0·41	0·41		

* $P=0·001$; † $P=0·01$; ‡ $P=0·02$; § $P=0·05$

shown in Tables 1 and 2. Analysis of the results showed no significant variation from the normal in the total protein or beta globulin and only slight variations in the alpha 2 and gamma globulin. In all groups the albumin levels were significantly lower than in the controls. The alpha 1 globulin was significantly raised in the cases with chronic diarrhoea and undernutrition. The pattern was similar in all the abnormal groups; a depression in albumin levels was the most striking feature with a less pronounced increase in alpha 1 globulin. The rather higher albumin levels in the infants with chronic respiratory infection was probably due to the older age in this group.

The group with chronic diarrhoea also showed the most marked loss of weight as measured by the percentage of expected weight at the time of their first attendance.

The distribution of the amino-acid curves and the titre of duodenal trypsin in the various groups were also established, and are shown in Table 3. Only two infants with chronic diarrhoea had normal

curves and all had trypsin titres of under 1: 200. The findings in cases with acute diarrhoea markedly resembled those in chronic respiratory infection and these cases did not show the marked impairment of pancreatic function of the infants with chronic diarrhoea. Unfortunately not all the cases of under-nutrition were intubated and only 13 had amino-acid

TABLE 3

DISTRIBUTION OF TRYPSIN TITRE AND RESULTS OF AMINO-ACID ABSORPTION CURVES

| No. of Cases | Amino-acid Curve | | Trypsin Titre | | |
	Normal	Abnormal	Under 1:200	1:200	Over 1:200
16 Undernutrition* ..	4	9	2	1	5
9 Acute diarrhoea ..	4	5	—	2	7
13 Chronic diarrhoea	2	11	13	—	—
9 Respiratory infection	4	5	—	3	6

* In this group eight infants were intubated and 13 had amino-acid curves.

TABLE 2

SERUM PROTEIN PATTERN IN NORMAL INFANTS AND IN INFANTS WITH NUTRITIONAL DISTURBANCES
(PERCENTAGE VALUES)

| | Albumin | Globulins | | | | | % of Expected Weight |
		α_1	α_2	Total α	β	γ	
Normals	59·8	5·1	13·2	18·3	12·1	9·6	
S.D.	1·4	1·3	1·4	2·1	1·7	2·3	
Undernutrition	50·8	7·7	14·4	22·1	14·0	13·0	73·3
S.D.	6·5	3·1	4·2	5·7	2·9	6·7	
Acute diarrhoea	53·1	6·6	15·4	22·0	13·4	11·2	79·3
S.D.	6·7	2·2	2·8	4·0	3·6	1·7	
Chronic diarrhoea	49·2	8·6	16·3	24·9	13·7	12·0	69·9
S.D.	5·5	3·4	3·9	5·8	4·0	4·3	
Respiratory infections	52·7	6·2	15·4	21·6	12·5	12·7	82·2
S.D.	4·8	1·9	4·6	4·4	2·8	5·6	

curves. From the available results it appears that with regard to pancreatic function this group lay between those infants with chronic diarrhoea and the other two groups. In only one case of chronic diarrhoea was tryptic activity present in a titre of over 1:50 and in four infants no activity could be detected.

The relationship of the percentage of serum albumin to the percentage of expected weight and to the titre of duodenal trypsin is shown in Table 4.

TABLE 4

RELATIONSHIP OF PERCENTAGE SERUM ALBUMIN TO PERCENTAGE OF EXPECTED WEIGHT AND TITRE OF DUODENAL TRYPSIN

				% Albumin	No. of Cases
% Expected weight					
Below 70%	..	..	..	48·8	12
70–80%	..	..	..	52·7	25
Over 80%	..	..	..	50·1	10
Titre of trypsin					
Below 1:200	..	..		48·5	15
1:200	..	..		50·3	6
Over 1:200	..	..		53·5	18

The figures for the relation between the titre of duodenal trypsin and the percentage of serum albumin are somewhat misleading. From them it might be assumed that the two bore a direct relation to each other. Whilst in general infants with very low or absent trypsin had low albumin levels there were exceptions to this and some infants with satisfactory trypsin titres had albumin levels of under 50%. The level of serum albumin does not therefore appear to be directly related either to the weight loss or to the degree of pancreatic dysfunction.

Discussion

Consideration of the results makes it clear that whatever the primary cause of the failure to thrive, the changes in the protein pattern are similar, the differences being of degree rather than of quality. The albumin showed a marked fall in all groups, alpha globulin showed a slight increase over normal values and gamma globulin tended to increase. These findings are in agreement with those of other authors who have determined the serum protein pattern in chronic nutritional disturbances. Gollan (1948) reported low albumin and raised globulins in chronic malnutrition in infants but he did not fractionate the globulins. Burgio and Giacalone (1953), investigating infants with nutritional atrophy, reported low albumin values with a striking increase in alpha globulin. Yoshida (1953) found low albumin levels and raised alpha and gamma globulin fractions. Jaso, Iturriaga and Roldan (1954)

studied two groups of infants, cases of toxicoses (i.e. acute gastro-enteritis) and cases of nutritional dystrophy. In both groups the albumin was low and alpha and gamma globulins raised compared with the normal. Carletti (1955) found low albumin and increased alpha globulins in both acute and chronic nutritional disturbances. The gamma globulin was either normal or elevated. Hallman, Kauhito, Louhivuori and Uroma (1952), Homolka and Mydlil (1955), and Schiavini and Sacconaghi (1956) investigated cases of acute gastro-enteritis, and these workers all found lowered albumin, raised alpha globulin and occasionally raised gamma globulin. Lubchez (1948) described the serum protein changes in a variety of infections in childhood. These were similar to those reported above. The changes in the serum protein pattern seem to be essentially similar in infants with nutritional disturbances whatever the primary cause. Grossman, Sappington, Burrows, Lavietes and Peters (1945) and Peters (1946) have stated that pyrexia *per se* does not cause nitrogen loss. Nevertheless, large amounts of nitrogen are lost during acute illnesses, and this loss is continued after the temperature has returned to normal. This factor cannot be ignored when considering the hypoalbuminaemia of acute infection. Madden, Winslow, Howland and Whipple (1937) found that sterile turpentine abscesses markedly inhibited the regeneration of plasma proteins in animals depleted by plasmaphoresis even when given an adequate diet. They suggested a disturbance of the synthesizing mechanism as a cause for this failure.

There is considerable controversy over the state of pancreatic function in nutritional disorders in infancy. All authorities agree that enzyme secretion is depressed in severe protein malnutrition (Veghelyi, 1948; Thompson and Trowell, 1952; Dean and Schwartz, 1954; Gomez, Galvan, Cravioto and Frenk, 1954; Mukherjee and Werner, 1954; Scrimshaw, Behar, Perez and Viteri, 1955). From reports dealing with infants with other conditions it appears that pancreatic enzymatic activity is often depressed in acute and chronic diarrhoea and sometimes during respiratory infections. This depression is often selective, one enzyme being present in normal amounts whilst the other two show lowered values or are absent (Hess, 1913; Davison, 1925; Farber, Schwachman and Maddock, 1943; McDougall, 1950). This demonstrates the need to examine the activity of all three pancreatic enzymes in the duodenal juice in suspicious cases and not to rely merely on a trypsin estimation as is the procedure in many centres. McDougall (1950) reported normal enzyme activity in 18 children with

severe malnutrition. She did not report on the serum protein patterns but Gomez *et al.* (1954) and Mukherjee and Werner (1954), both working with infants with protein malnutrition, correlated the level of pancreatic enzyme activity with the serum albumin level. Gomez *et al.* noted no correlation, but Mukherjee and Werner found a significant correlation between amylase activity and serum albumin, and at albumin levels below 2·5 g.% a linear regression existed between the two. The bulk of evidence suggests that pancreatic exocrine function may be depressed in a variety of chronic nutritional disturbances in infancy, especially if these are associated with alimentary or respiratory infections. Such pancreatic depression is less likely to occur in acute disorders of sudden onset. Matsaniotis (1957) criticized the use of amino-acid curves after a protein meal as a test for pancreatic function because abnormally low values were not necessarily due to diminished output of pancreatic enzymes but might reflect impaired absorption or abnormal rates of amino-acid uptake by the tissues. In a series of infants with simple inanition he found normal absorption after a meal of casein hydrolysate, and normal removal rates of amino-acid from the blood after intravenous hydrolysates. As a result of this work he stated that the proteolytic activity in the gastro-intestinal tract of infants with this type of undernutrition was not impaired.

The infants in the present series had evidence of chronic protein deficiency as shown by depression of the serum albumin, muscular wasting and recovery on a high protein diet. Prolonged inadequacy of the diet from whatever cause must lead to lowered protein intake, and this in turn is responsible for diminished output of proteolytic enzymes and thus available dietary protein becomes even less adequate. Confirmatory evidence that these infants were protein-deficient lay in the fact that the serum protein patterns remained abnormal until satisfactory weight gains had been made. This often took several weeks of high protein feeding. Platt (1958) demonstrated clearly the difference in the clinical picture in cases of protein malnutrition with a high carbohydrate intake where the picture of kwashiorkor is seen, and in cases where protein deficiency accompanies a low carbohydrate intake and a marasmic type of malnutrition results. The type of malnutrition seen in this series and in most cases in this country does not lead to florid clinical signs and for this reason often passes unrecognized; a symptomatic diagnosis of chronic gastro-intestinal disorder is applied and the progress is slow and unsatisfactory. The serum protein pattern shows non-specific changes in these disorders and the level of serum albumin does not bear a direct relationship to the pancreatic enzyme activity, though in general the most severely affected infants showed the lowest levels.

Summary

The serum protein pattern in 20 normal infants and in 47 infants with nutritional disturbances was examined by paper electrophoresis. The albumin fraction was significantly lower than normal in all the infants who had failed to thrive regardless of the aetiology of their condition. The alpha and gamma globulins tended to be higher than normal, the beta globulin and total protein showed no change. The group of infants with chronic diarrhoea showed the most pronounced changes in the protein pattern and also the most severe loss of weight. This group also had the most marked depression of pancreatic function but no definite correlation between serum albumin, percentage of expected weight or titre of duodenal trypsin could be established. The serum protein pattern is of no help in specific diagnosis in infants who fail to thrive, the changes being non-specific.

REFERENCES

Bate, J. G. and James, U. (1956). Proteolytic activity of the pancreas. *Arch. Dis. Childh.*, **31**, 506.
Block, R. J., Durrum, E. L. and Zweig, G. (1955). *A Manual of Paper Chromatography and Paper Electrophoresis.* New York, Academic Press Inc.
Burgio, G. R. and Giacalone, O. (1953). Elettroforetici reperti nella distrofia del lattante. *Boll. Soc. ital. Biol. sper.*, **29**, 695.
Carletti, B. (1955). Determinazione elettroforetica delle sieroproteine nei disturbi acuti e cronici della nutrizione nell'infanzia. *Minerva pediat. (Torino)*, **7**, 1127.
Davison, W. C. (1925). Duodenal contents of infants in health and during and following diarrhoea. *Amer. J. Dis. Child.*, **29**, 743.
Dean, R. F. A. and Schwartz, R. (1954). The effects of protein deficiency in young children. *Courrier*, **4**, 293.
Farber, S., Schwachman, H. and Maddock, C. L. (1943). Pancreatic function and disease in early life. I. Pancreatic enzyme activity and the celiac syndrome. *J. clin. Invest.*, **23**, 827.
Flynn, F. V. and De Mayo, P. (1951). Micro-electrophoresis of protein on filter-paper. *Lancet*, **2**, 235.
Gollan, F. (1948). Blood and extracellular fluid studies in chronic malnutrition in infancy. *J. clin. Invest.*, **27**, 352.
Gomez, P. F., Galvan, R. R., Cravioto, J. and Frenk, S. (1954). Studies on the undernourished child. XI. Enzymatic activity of the duodenal contents in children affected with third degree malnutrition. *Pediatrics*, **13**, 548.
Grossman, C. M., Sappington, T. S., Burrows, B. A., Lavietes, P. H. and Peters, J. P. (1945). *J. clin. Invest.*, **24**, 523.
Hallman, N., Kauhito, J., Louhivuori, A. and Uroma, E. (1952). Electrophoretic studies of plasma proteins in severe infantile gastroenteritis. *Scand. J. clin. Lab. Invest.*, **4**, 89.
Hess, A. F. (1913). II. The pancreatic ferments in infants in acute intestinal indigestion (alimentary intoxication). *Amer. J. Dis. Child.*, **5**, 268.
Homolka, J. and Mydlil, V. (1955). The blood protein picture in diarrhoea of infants in comparison with other diseases. *Ann. Paediat. Basel*, **185**, 142.
Jaso, E., Iturriaga, E. and Roldan, M. A. (1954). Alteraciones de las proteins plasmaticas en el curso do los transtornos nutritivos del lactante. *Rev. esp. Pediat.*, **10**, 213.

Levin, B. and Oberholzer, V. G. (1953). Paper electrophoresis of serum proteins. *Amer. J. clin. Path.*, **23**, 205.

Lubchez, R. (1948). Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. *Pediatrics*, **2**, 570.

McDougall, Clarice (1950). Clinical evaluation of normal enzyme content in the pancreatic juice of children. *Pediatrics*, **5**, 114.

Madden, S. C., Winslow, P. M., Howland, J. W. and Whipple, G. H. (1937). Blood plasma protein regeneration as influenced by infection, digestive disturbances, thyroid and food proteins. *J. exp. Med.*, **65**, 431.

Matsaniotis, N. S. (1957). Studies on protein metabolism in under-nourished infants and children. *J. Pediat.*, **51**, 367.

Mukherjee, K. L. and Werner, G. (1954). Enzyme activity and protein concentration in the serum of patients with malnutrition. *J. Lab. clin. Med.*, **43**, 727.

Peters, J. P. (1946). Nitrogen metabolism in acute and chronic disease. *Ann. N.Y. Acad. Sci.*, **47**, 327.

Platt, B. S. (1958). Malnutrition and the pathogenesis of disease. *Trans. roy. Soc. trop. Med. Hyg.*, **52**, 189.

Schiavini, C. A. and Sacconaghi, E. (1956). Considerazione sul comportamento elettroforetico delle sieroproteine nelle gastro-enteriti acute infantili. *Minerva pediat.* (*Torino*), **8**, 393.

Scrimshaw, N. S., Behar, M., Perez, C. and Viteri, F. (1955). Nutritional problems of children in central America and Panama, *Pediatrics*, **16**, 378.

Thompson, M. D. and Trowell, H. C. (1952). Pancreatic enzyme activity in duodenal contents of children with a type of kwashiorkor. *Lancet*, **1**, 1031.

Veghelyi, P. V. (1948). Proceedings 5th International Congress of Paediatrics, New York, 1947. *Acta paediat. Uppsala*, **36**, 128.

West, C. D., Wilson, J. L. and Eyles, R. (1946). Blood amino nitrogen levels; changes in blood amino nitrogen levels following the ingestion of proteins and of protein hydrolysate in infants with normal and with deficient pancreatic function. *Amer. J. Dis. Child.*, **72**, 251.

Yoshida, H. (1953). Electrophoretic analysis of serum protein of children with or without nutritional dystrophy. *Tôhoku J. exp. Med.*, **57**, 205.

EFFECT OF TRIIODOTHYROACETIC ACID ON THE ELECTROCARDIOGRAM IN CRETINISM

BY

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The purpose of this note is to report the effect of the acetic acid derivative of triiodothyronine (Triac) on the electrocardiogram (E.C.G.) in cretinism. It is well recognized that myxoedema in the adult and cretinism in the infant lead to an abnormal E.C.G. characterized by a low voltage curve, particularly affecting the T waves, and prolongation of the Q–T interval. On treatment with thyroid these changes disappear. Evans (1956) writes that the E.C.G. becomes normal after three weeks' therapy and that 'the adequate dosage of thyroid may be estimated from watching it reinstate and maintain a normal cardiogram'.

1-3: 5: 3-Triiodothyroacetic acid has an immediate effect on the basal metabolic rate and body temperature in hypophysectomized rats (Donhoffer, Várnai and Sziebert-Horváth, 1958). It has a rapid effect on the basal metabolic rate in myxoedema (Trotter, 1955). Ibbertson, Fraser and Alldis (1959) have shown that it causes a rapid change towards normal in the E.C.G. of adults with myxoedema. They also state that 'in a 5-month-old cretin, at eight hours after 0·5 mg. of triac by mouth, there was an obvious increase in the R and T waves of the E.C.G.'. The effect on the E.C.G. in two infants with cretinism is recorded in this paper.

Case Reports

Case 1. This boy was seen at the age of 12 weeks. He was the second child of a Rh positive mother, the other child being a boy aged 16 months who was alive and well, and had no jaundice at birth. The mother had an antepartum haemorrhage one month before delivery. The baby was born three weeks before the expected date of delivery with a birth weight of 4 lb. 13 oz. He was breast fed for four weeks and then fed on Ostermilk. The baby had been slightly jaundiced since the second or third day of life, but the stools had always been rather light yellow in colour. The urine had always been dark.

On examination the baby had a rather harsh cry, moderate jaundice of the skin and conjunctivae, an umbilical hernia, and small right and left inguinal herniae. The liver was palpable two finger breadths below the costal margin and the tip of the spleen was palpable. The skin was rather dry, scaly and greasy, especially over the face, and the tongue protruded (Fig. 1). Blood pressure was 70 mm. systolic by the flush method.

The child weighed 10 lb. 3 oz. (4·625 kg.), length 21 in. (53·3 cm.).

Haemoglobin was 12 gm.%, reticulocytes 4%.

FIG. 1.—Case 1.

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FIG. 2.—Case 1, aged 12 weeks.   Radiograph of wrist.

Case I

Lead II

Lead A.V.F.

Before   4 hrs.   8 hrs.   12 hrs.   20 hrs.
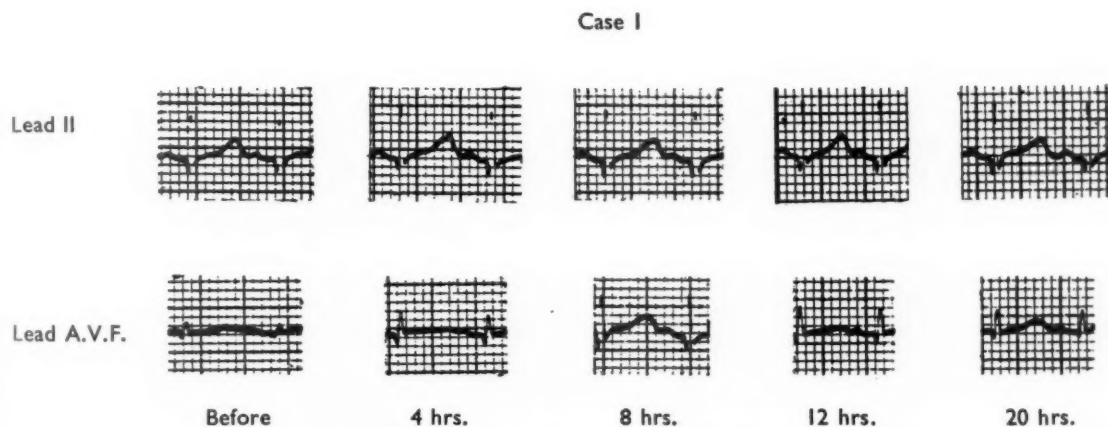
FIG. 3.—Case 1.   E.C.G.s before and after Triac (1 mg. given two-
hourly for four doses).   Timings are in hours after first dose.

FIG. 4.—Case 1, aged 12 months.   Radiograph of wrist.

Radiographs showed a retarded bone age (Fig. 2) and a poorly formed first lumbar vertebra.

The clinical diagnosis of cretinism was clear.

Triac was given in 1-mg. doses at two-hourly intervals for four doses. E.C.G.s were recorded before and after, the timings being given from the time of the first dose (Fig. 3).

Response to treatment with thyroid extract B.P. confirmed the diagnosis of cretinism, clinical and radiological (Fig. 4), progress being normal during the following year.

Case 2. This girl was first seen at the age of 6 months. She was the first child, born at full term after a normal pregnancy, the birth weight being 6 lb. 12 oz. From the age of $4\frac{1}{2}$ months she was noticed to be sluggish, sleeping excessively and not to be making progress. On examination she was an obvious cretin (Fig. 5). Radiographs showed a retarded bone age and poor development of the upper part of the body of the second lumbar vertebra (Fig. 6).

This patient was given 4 mg. Triac in one dose. E.C.G.s were recorded before and after the test dose (Fig. 7).

FIG. 5.—Case 2.
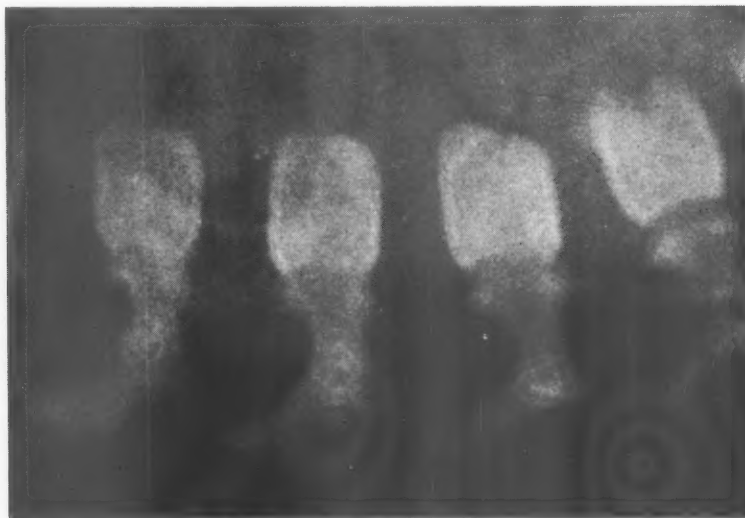
FIG. 6.—Case 2, aged 6 months. Lateral radiograph of lumbar spine.

Response to treatment with thyroid extract B.P. confirmed the diagnosis of cretinism and progress over the next six months was normal.

Normal Infants. A 4-mg. dose of Triac has been given to each of three infants with no endocrine disorder and a normal E.C.G. pattern. Small variations in the magnitude of the complexes were found on successive recordings even when great care was taken over standardization. There were, however, no changes in voltage comparable in magnitude to that observed in Case 2 described above.

Case 2
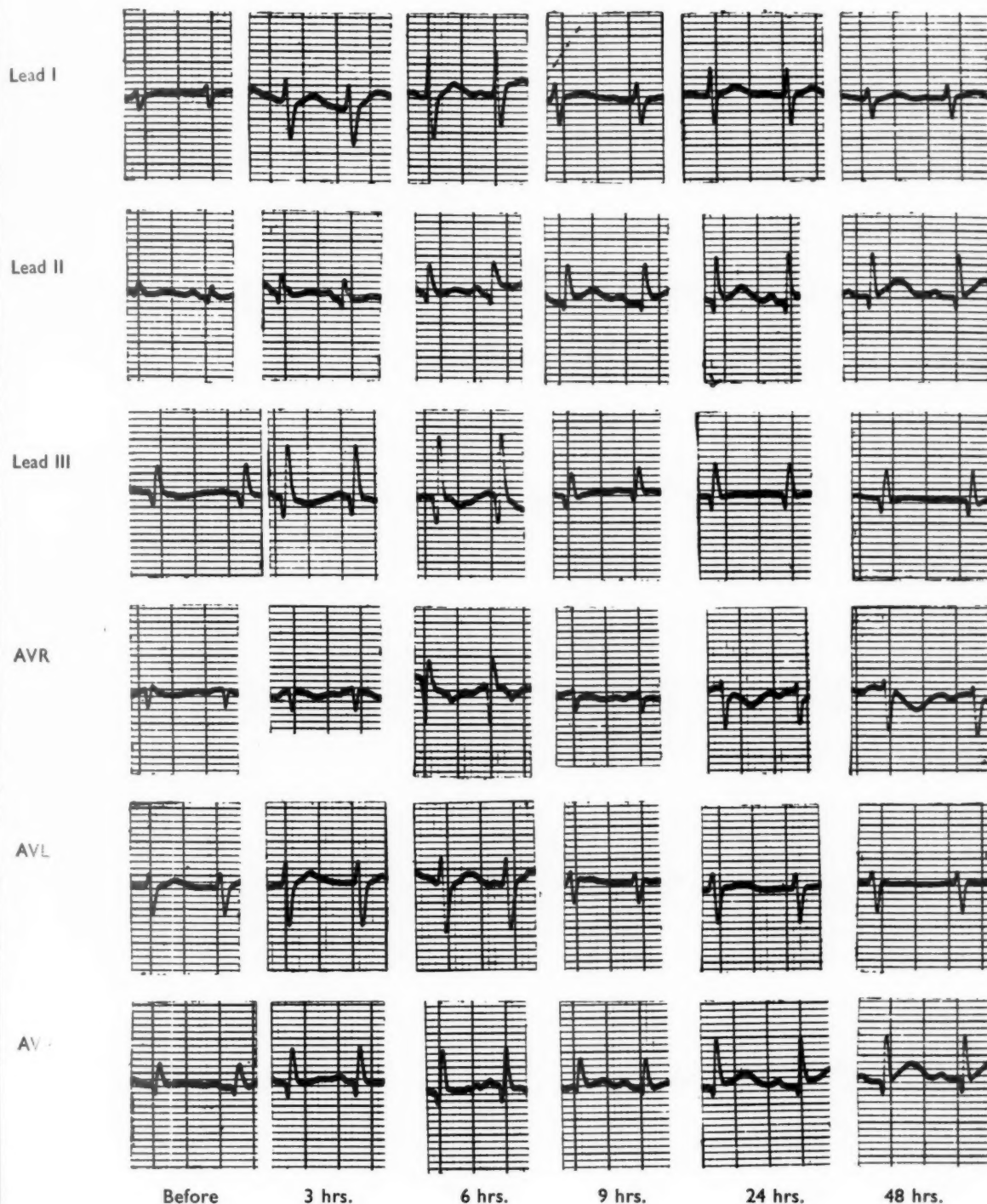
FIG. 7.—Case 2.   E.C.G.s before and after Triac (4 mg. given in one dose).   Timings are in hours after administration of Triac.

Comment

Care was taken to ensure that the standardization of the E.C.G. machine* was correct and similar for each tracing.   The main change noted in the E.C.G.s of cretins was an increase in the voltage.   The response was not as marked in the first patient, to whom the triiodothyroacetic acid was given in divided doses over a six-hour period, as in the second patient, to whom a large single dose was given. In the latter case the response was unequivocal; the E.C.G. did not return completely to its previous low voltage pattern even after three days.   Whether this test will be of significant value in the diagnosis of less obvious cases of cretinism is doubtful since in them the initial electrocardiogram will often not be significantly abnormal.

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* Cambridge Electrite Model Portable Electrocardiograph.

Summary

The effect of triiodothyroacetic acid on the electrocardiogram in cretinism is described.

REFERENCES

Donhoffer, S., Várnai, I. and Sziebert-Horváth, E. (1958).   Immediate effect of 1–3:5:3′-Tri-iodothyroacetic acid on metabolic rate and body temperature in hypophysectomized rats and the actions of cortisone.   *Nature (Lond.)*, **181**, 345.
Evans, W. (1956).   *Cardiology*.   2nd ed.   Butterworth, London.
Ibbertson, K., Fraser, R. and Alldis, D. (1959).   Rapidly acting thyroid hormones and their cardiac action.   *Brit. med. J.*, **2**, 52.
Trotter, W. R. (1955).   Effect of Triiodothyroacetic acid in a case of myxoedema.   *Lancet*, **2**, 374.

IRON-DEFICIENCY ANAEMIA BETWEEN 3 MONTHS AND 2 YEARS OF AGE AND A COMPARISON OF TREATMENT WITH FERROUS SULPHATE AND FERROUS FUMARATE

BY

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A recent paper from this hospital (Morrison, Bass, Davis, Hobson, Madsen and Masters, 1957) reported that about one half of the children under 2 years of age admitted because of acute respiratory infections had haemoglobin concentrations below 11 g. per 100 ml. The purposes of the present investigation were to determine the distribution of the haemoglobin levels in children between 3 months and 2 years of age attending the hospital, to compare two forms of iron treatment and to observe whether infection influenced the response to therapy.

For many years ferrous sulphate (iron content about 33% of exsiccated salt) has been the compound most widely prescribed for the treatment of iron deficiency anaemia. In a small number of patients this causes gastro-intestinal disturbance. The claim has been made that organic compounds of iron are better tolerated. Recently ferrous fumarate, a compound with the empirical formula $FeC_4H_2O_4$, has been advocated (*Lancet*, 1958). The iron content of ferrous fumarate (about 33% iron) is higher than that of ferrous gluconate (about 12% iron) or ferrous succinate (about 25% iron).

Selection of Patients

It was intended to include in the survey of haemoglobin levels the values found in all children between 3 months and 2 years of age attending the casualty department with a new complaint or admitted to the medical ward between January 19, 1958 and March 31, 1958. Owing to the large number of children who attended the casualty department, pressure of work made it necessary to include casualty attendances during the morning only for much of the period. One hundred and three children attending the casualty department and 53 admitted to the medical ward were included in the survey. Seventy-three children with haemoglobin levels below 11 g. per 100 ml. were observed in the assessment of therapy. Forty-seven of these children were initially seen in the survey and 26 after the survey period ended.

Methods

Approximately 0·4 ml. of capillary blood was collected from each patient into a Pasteur pipette containing dried heparin. The sample was ejected into a small tube, well mixed and immediately used to fill pipettes for estimation of haemoglobin, packed cell volume and erythrocyte sedimentation rate (E.S.R.). The haemoglobin was estimated by the oxyhaemoglobin method described by Dacie (1956). An Ilford 0·5 neutral density screen was read with each series of estimations. Its equivalent haemoglobin value was determined by using blood of known haemoglobin content supplied by Messrs. Keeler Ltd. Each pipette was calibrated. The packed cell volume (P.C.V.) was estimated using capillary tubes spun in a Hawksley microhaematocrit centrifuge at 12,000 g. for five minutes. The E.S.R. was estimated using a tube of 1·5 mm. bore and a column of blood 100 mm. long.

Three mixtures (A, B and C) were prepared; none of the medical staff knew which was issued to a particular child, the records being kept by the pharmacist:

A. Ferrous fumarate in a flavoured suspension containing 75 mg. (equivalent to 25 mg. elemental iron) per 4 ml.

B. Ferrous sulphate in a flavoured vehicle similar to that used for Ferrous Sulphate Mixture for infants (British National Formulary, 1957) modified to contain 120 mg. hydrated salt (equivalent to 25 mg. elemental iron) per 4 ml.

C. A placebo consisting of the flavoured vehicle without ferrous sulphate.

The placebo was given to every third child with a haemoglobin level between 9 and 11 g. per 100 ml. presenting in four consecutive weeks of the study in order to have a control group for comparison of side-effects and

spontaneous haemoglobin changes. It was not felt wise to give the placebo to children with a haemoglobin level below 9 g. per 100 ml.

In order to ensure comparability as regards haemoglobin levels and age in the children given ferrous sulphate and ferrous fumarate, the children were allotted to one of four groups:

3 months-1 year
1 year-2 years } haemoglobin 9-11 g. per 100 ml.

3 months-1 year
1 year-2 years } haemoglobin under 9 g. per 100 ml.

The mixtures were given in rotation to the patients in each group according to the order of arrival of the prescriptions in the pharmacy.

All mixtures were issued with plastic measuring spoons (4 ml. capacity) and the following instructions:

'One teaspoonful after food once a day for 3 days, twice a day for the next 3 days, then three times a day.'

The mother was asked to bring the child back two weeks and four weeks after the start of treatment. On the first return visit she was given another bottle of the same medicine. On each visit the doctor reassessed the child's condition and asked whether any vomiting, diarrhoea or constipation had occurred since the previous visit. Any comments provided by the mother about the child's reaction to the medicine were noted.

Results

Haemoglobin Levels. Fig. 1 shows the total number of children with haemoglobin levels in each one-gramme range. There is a skew distribution in which 20% of the children have haemoglobin levels
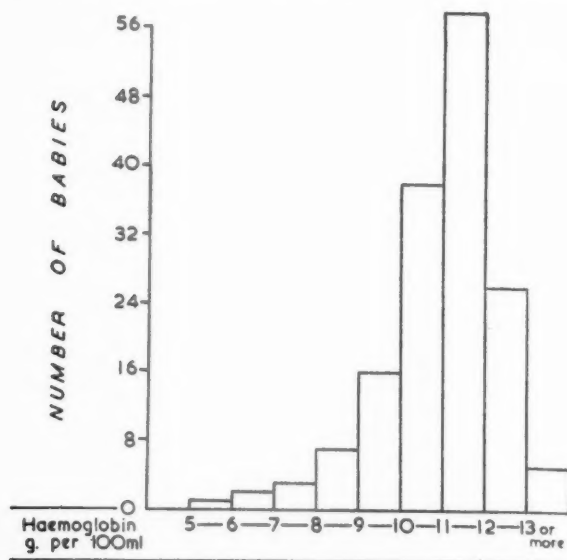
FIG. 1.

of 12 g. per 100 ml. or more, 37% have between 11 and 12 g. per 100 ml. and 43% have under 11 g. per 100 ml. Of the children requiring admission to the medical ward, 53% had haemoglobin levels below 11 g. per 100 ml., a finding similar to that of Morrison *et al.* (1957).

Table 1 gives the averages of the mean corpuscular

TABLE 1

CORRELATION OF MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATIONS WITH HAEMOGLOBIN LEVELS

Haemoglobin range (g. per 100 ml.)	Under 9	9-10	10-11	11-12	12 or more
Mean M.C.H.C. (%) ..	27·1	30·2	31·2	32·4	32·5
No. of patients	13	15	38	56	27

haemoglobin concentrations (M.C.H.C.) of the children in each one-gramme range of haemoglobin level. The progressive reduction in average M.C.H.C. in the lower haemoglobin ranges indicates an iron-deficiency factor.

Table 2 gives the average E.S.R. of the children in

TABLE 2

CORRELATION OF ERYTHROCYTE SEDIMENTATION RATES WITH HAEMOGLOBIN LEVELS

Haemoglobin range (g. per 100 ml.)	Under 9	9-10	10-11	11-12	12 or more
Mean E.S.R. (mm./hr) ..	30	29	20	16	13
No. of patients* ..	13	16	38	58	31

* The numbers of patients are different from those in Table 1 as the M.C.H.C. was not determined in every patient in whom an E.S.R. was observed and who was included in the survey.

each one-gramme range of haemoglobin level. There is a rise in average E.S.R. from the highest haemoglobin range downwards. Iron deficiency anaemia alone may not cause a rise in the E.S.R. (Terry, 1950); several children in the survey with haemoglobin levels below 9 g. per 100 ml. had E.S.R.s of less than 10 mm. in one hour.

Assessment of Iron Therapy. Table 3 shows the acceptability of the three medicines (A, B and C). Only about one third as many children received the placebo as received either of the iron mixtures. A liking for the medicine was remarked by the mothers in a majority of children receiving the placebo and only in a few of the children receiving the iron mixtures. A distaste for the medicine was confined to the children receiving the iron mixtures and was slightly more frequent in children receiving

TABLE 3

COMPARISON OF ACCEPTABILITY OF MEDICINES

	Ferrous Fumarate	Ferrous Sulphate	Placebo
Totals allocated to treatment group*	31	31	11
Number returning once	24	27	9
Number returning twice ..	22	22	7
Number liking medicine ..	3	4	5
Number disliking medicine ..	4	10	0
Vomiting	1	0	0
Diarrhoea	1	0	1
Constipation	3	4	2

* Includes nine babies who did not complete their course of medicine.

ferrous sulphate. Vomiting, diarrhoea or constipation were noted in only a small proportion of children. A comparison of their incidence in the iron-treated groups and placebo group reveals no evidence that these symptoms were related to the administration of either iron mixture. There were no other symptoms attributable to the iron mixtures.

Table 4 compares the haemoglobin responses to

TABLE 4

COMPARISON OF HAEMOGLOBIN RESPONSE TO EACH MEDICINE IN PATIENTS WITH INITIAL HAEMOGLOBIN LEVELS BETWEEN 9 AND 11 g. PER 100 ml.

	Mean Haemoglobin (g. per 100 ml.)		
	Ferrous Fumarate	Ferrous Sulphate	Placebo
Initially	10·1*	10·0*	10·3*
After 2 weeks	10·8	11·0	10·6
After 4 weeks	11·5	11·3	10·7
Rise after 4 weeks	1·4	1·3	0·4
Number of patients	14	15	7

* There is no significant difference between the initial haemoglobin levels in the groups receiving iron therapy and the placebo group (p > 0·10). The mean change in haemoglobin level of those children receiving either type of iron therapy is significantly greater than of those receiving the placebo (p < 0·01).

the three medicines in the slightly anaemic children. The mean responses to the two iron mixtures were almost equal and considerably more than the change occurring in the group receiving the placebo.

Table 5 compares the haemoglobin and M.C.H.C.

TABLE 5

COMPARISON OF HAEMOGLOBIN AND M.C.H.C. RESPONSE TO EACH MEDICINE IN PATIENTS WITH INITIAL HAEMOGLOBIN LEVELS BELOW 9 g. PER 100 ml.

	Mean Haemoglobin (g. per 100 ml.)		Mean M.C.H.C. (%)	
	Ferrous Fumarate	Ferrous Sulphate	Ferrous Fumarate	Ferrous Sulphate
Initially	6·8	8·0	25·8	27·5
After 2 weeks ..	8·7	9·6	26·4	27·5
After 4 weeks ..	10·4	10·4	27·5	29·4
Rise	3·6	2·4	1·7	1·9
No. of patients ..	8	7	7	7

responses to the two iron mixtures in the children with initial haemoglobin levels below 9 g. per 100 ml. There was a good response to both iron mixtures. As would be expected, the response to iron therapy is greater when the haemoglobin level is lower. The response is noticeable even when the initial haemoglobin level is between 10 and 11 g. per 100 ml., the average rise in these patients being just over 1 g. per 100 ml.

Table 6 is an attempt to assess whether the infections found in the slightly anaemic children and the course they took influenced the response to iron therapy. It can be seen that there was no substantial difference between the haemoglobin responses in the groups selected on the basis of E.S.R. patterns.

Summary

Anaemia is still a common finding in young children attending this hospital. The anaemia

TABLE 6

CORRELATION OF E.S.R. LEVELS WITH RESPONSE TO IRON THERAPY IN BABIES WITH HAEMOGLOBIN LEVELS INITIALLY 9-11 g. PER 100 ml.

No. of Babies	E.S.R. Group*		Response to Iron Therapy						
	Description	Mean E.S.R. Values (mm.)			Mean Haemoglobin (g. per 100 ml.)				
		Initial	2 weeks	4 weeks	Initial	2 weeks	4 weeks	Mean Rise
	All E.S.R.s under 15 mm./hr.	3	7	6	10·2	10·8	11·8	1·6
	Final E.S.R. at least 15 mm./hr. less than initial E.S.R. ..	41	18	13	10·0	11·0	11·2	1·2
	Remainder	17	13	19	9·7	10·4	10·9	1·2

* If a high E.S.R. is taken to indicate infection and a fall improvement of infection, the first group would be babies with slight infection, the second with an improving infection and the third with continuing infection.

usually responds to oral iron therapy, whether given as a ferrous sulphate or a ferrous fumarate mixture, both being generally palatable. The presence of a persistently raised E.S.R. (an indication of infection) is not associated with a substantial reduction in the response to iron therapy.

REFERENCES

Dacie, J. V. (1956). *Practical Haematology*, 2nd ed. Churchill, London.
Lancet (1958). Iron deficiency in man, 1, 1162.
Morrison, B., Bass, D., Davis, J. A., Hobson, D., Madsen, T. I. and Masters, P. L. (1957). Acute lower-respiratory infections in childhood. *Lancet*, 2, 1077.
Terry, R. (1950). Erythrocyte sedimentation in anaemia, *Brit. med. J.*, 2, 1296.

THE SIGNIFICANCE OF ONE UMBILICAL ARTERY

BY

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Absence of one umbilical artery is a rare finding, usually associated with other severe congenital malformations. The earliest recorded case is attributed to Casp. Bauhin in 1621, although Noortwyck (1743) quotes Vesalius' description *'unam tantum arteriam in fune Fallopius vidit'*. Otto (1830) collected 41 case reports from the literature, and Hyrtl (1870) described 14 cases of his own and found 16 more in the literature. Browne (1925) referred to one case with a single artery and numerous capillaries replacing the vein. Benirschke and Brown (1955) described 55 cases, and Richart and Benirschke (1958) described one further case with gonadal dysgenesis. Javert and Barton (1952) examined the umbilical cord of 297 aborted foetuses of four months' gestation and found one with a single artery. Of the 182 cases of sympodia collected by Ballantyne (1898), Kampmeier (1927) and Hendry and Kohler (1956), 95 had a single artery in the umbilical cord, and in the remainder the cord was not examined. Schatz (1900) found 11 cases among 46 acardiac monovular twins and three acardiac monovular triplets. There is therefore clearly a high incidence in acardiac foetuses and sympodia. In foetuses without acardia or sympodia the incidence appears to be relatively low, and only Javert and Barton (1952) provide data from which an assessment can be made.

This paper describes 11 cases encountered among routine autopsies performed at the Birmingham Children's Hospital from March, 1958, to February, 1959, in autopsies on 159 stillbirths and 252 live born babies of 8 weeks of age or less. Severe malformations were found in nine (81%) and in 2% of the controls.

Case Reports

Case 1. A female baby was stillborn at 36 weeks' gestation to a para 1 mother aged 20. There had been a threatened abortion at 3 months.

Autopsy showed rotation of the trunk through 90° so that the buttocks were facing the left side, and a large hernia into the body stalk. The sac was formed by amnion and contained liver and loops of bowel. The lungs were hypoplastic and abnormally lobed. The heart showed a defect in the membranous part of the ventricular septum. The right renal artery arose from the proximal part of the superior mesenteric artery. The umbilical artery entered the right internal iliac artery and was wider than normal. The small intestine was short (97 cm.) and was strangulated distally in the hernial sac. The brain showed bilateral cirsoid aneurysms of the Sylvian fissures with focal microgyria and encephalomalacia of the underlying cerebral tissue on the right side. The placenta weighed 237 g. and was normal. The umbilical cord lay in the wall of the hernial sac and was short (14·5 cm.). It contained one artery and one vein throughout its length.

Case 2. A male baby was born at full term after a normal pregnancy. On the third day he had a surgical repair for oesophageal atresia with tracheal fistula and died six days later with respiratory obstruction and infection.

Autopsy showed repair of the tracheo-oesophageal fistula with oesophageal anastomosis. There was a diaphragmatic urethral valve at 0·9 cm. from the bladder neck. The bladder was dilated and hypertrophied and there was bilateral hydroureter and hydronephrosis. The right umbilical artery was absent and the right common iliac artery was narrow.

Case 3. A male infant was born at full term after a difficult delivery and died six hours later. The antenatal history was not known.

At autopsy there was gross radial deviation of the left thumb and radius. The small intestine was incompletely rotated and unfixed, and there was a Meckel's diverticulum. The right kidney and ureter were absent. The left kidney had two cortical cysts and the renal pelvis and ureter were dilated. The bladder was grossly dilated and hypertrophied and filled with heavily blood-stained fluid. There were lacerations of the bladder wall 2·5 and 3 cm. in length. The internal urethral orifice was stenotic and partially valved by mucous membrane, and beyond it the urethra was atretic. The testes were intra-abdominal and normal. The right renal artery was absent, and there were two left renal arteries. The left common iliac vessels were small, and the left umbilical artery was absent.

Case 4. A female baby was born at 35 weeks' gestation to a gravida 3 mother after a normal pregnancy. The baby died after one hour.

Autopsy showed low set ears and bilateral pes cavus. The external genitalia were abnormal, the main feature resembling a scrotum with a median dimple on its anterior surface. On either side of the scrotum were two folds resembling labia. The anus was represented by a shallow depression. There was oesophageal atresia, tracheo-oesophageal fistula and atresia of the duodenum. The small intestine showed a Meckel's diverticulum and lack of mesenteric fixation. The colon ended blindly on the posterior wall of the bladder. The liver showed abnormal lobulation of its inferior surface. The gall bladder was absent. The larynx and left bronchus were atretic and the left lung was absent. The heart had a high ventricular septal defect and a common truncus. There were two renal arteries on each side. The right umbilical artery was absent, and the right common iliac artery was smaller than the left. There was a persistent left superior vena cava. Both kidneys were small and cystic. There was duplication of the right ureter and renal pelvis. The two ureters were thin cords uniting caudally and ending blindly in the bladder wall. The left ureter and ureteric orifice were moderately dilated. The bladder was grossly dilated and hypertrophied. The internal urethral orifice was stenotic, and from it a hypoplastic urethra passed to the scrotal dimple. There were two normal ovaries but no uterus nor vagina.

Case 5. A male baby was stillborn at 31 weeks to a primigravida mother aged 20. The antenatal history was not known.

Autopsy showed coarse facial features with a depressed nasal bridge and low-set ears. There was a left diaphragmatic hernia, and the left pleural cavity was also continuous with the pericardial cavity. The heart showed atresia of the tricuspid valve and pulmonary infundibulum. The right ventricle was a minute blind chamber. There was a large atrial septal defect. The pulmonary arteries and ductus arteriosus were hypoplastic. The left umbilical artery was absent and the left common iliac artery was narrow. The right kidney and ureter were absent. The left kidney was hypoplastic and cystic. The left ureter was a thin cord with a normal ureteric orifice. The bladder was much dilated and hypertrophied. There was stenosis of the bladder neck, atresia of the prostatic urethra and agenesis of the prostate. The testes were intra-abdominal and normal. The lower end of the colon was atretic, ending blindly on the bladder wall. The termination of the spinal cord was abnormal. The cord extended to the lower end of the sacral canal and passed into a small skin-covered cartilaginous peg on its external aspect.

The placenta weighed 240 g. and was normal. The umbilical cord was normal apart from absence of one artery.

Case 6. A female baby was born at 36 weeks to a para 1 mother aged 17. The delivery was normal but the baby had white asphyxia and died after eight hours.

At autopsy the ears were low-set and the external genitalia were abnormal, represented by a median mound of soft tissue covered by skin. There was a sinus at the junction of the anus and the perineal skin. There was bilateral renal hypoplasia and agenesis of the bladder. The ureters were dilated to cystic proportions distally, and at the lower end of the uterus they communicated with the vagina which was continuous with the perianal sinus. The uterus was bicornuate, the ovaries were normal. The right umbilical artery was absent, and the right common iliac artery was very small. The lower part of the left umbilical artery gave rise to a vessel which crossed over to the right and divided into the right external and internal iliac arteries.

The placenta weighed 606 g. and was normal. The cord was excessively long (83 cm.).

Case 7. The first of monovular male twins was stillborn at 32 weeks to a para 1 mother, aged 25, after prolapse of the cord. The antenatal history was normal. The second twin died after 56 hours and had no malformations.

At autopsy the nose was slightly beaked and the ears were normal in position but had a soft flat helix. The kidneys were enlarged and cystic, fused together and low in position. The renal arteries consisted of several minute vessels arising close to the aortic bifurcation. The two ureters were very narrow and passed to a hypoplastic bladder. The urethra and testicles were normal. There was hypoplasia of the stomach, liver and lungs. The right umbilical artery was absent and the right common iliac was smaller than the left.

There was a diamniotic-monochorionic placenta weighing 362 g. The umbilical cords were attached near the central double amniotic membrane, one being normal and one having a single artery and vein. There were no demonstrable vascular anastomoses.

Case 8. The second of twins was stillborn at 38 weeks to a para 2 mother aged 22, after a normal pregnancy. The first was a female infant with no malformations who thrived normally.

Autopsy examination showed a sirenoid foetus with a single curved lower limb ending in a foot with three broad digits. The trunk consisted of a featureless mass surmounted by a head process. There was no definable perineum, vertebral column, thorax or abdomen, and no upper limbs. The umbilical cord was attached at the upper end of the trunk. The head process was covered by skin and had two auricular appendages on the right with an adjacent red polypoid process. A smear from the process showed epithelial cells with the chromatin pattern associated with the female sex. Internal examination was not performed.

There was a bulky monochorionic placenta weighing 760 g. One umbilical cord was normal and attached marginally. The other was thinner, contained one artery and one vein, and had a velamentous insertion.

Case 9. A female infant was born at full term to a primigravida mother aged 23, after a normal pregnancy.

At three weeks she developed heart failure, which did not respond to treatment and she died at six weeks.

At autopsy the heart was grossly enlarged. There was hypoplasia of the ascending aorta and the aortic arch with a narrow elongated aortic isthmus and a wide ductus arteriosus. There was a small defect in the upper posterior part of the muscular ventricular septum. The aortic valve was bicuspid. The right umbilical artery was absent and the right common iliac artery was narrow.

Case 10. A male infant was born at 31 weeks gestation after surgical induction of labour. The mother was a primigravida aged 25 with fulminating pre-eclamptic toxaemia. The infant died 10 minutes after birth.

At autopsy there were no congenital malformations. Much amniotic cellular debris was found in the lungs. The placenta was normal. The umbilical cord contained one artery and one vein and was otherwise normal.

Case 11. A male baby was stillborn at 41 weeks to a para 3 mother aged 22. The antenatal history was normal.

Autopsy examination showed a macerated baby with only one umbilical artery but no other congenital malformation. The placenta had a marginal infarct. The umbilical cord was normal apart from absence of one artery.

Discussion

There were 11 cases of single umbilical artery among 411 autopsies, an incidence of $2 \cdot 7\%$. There is no comparable perinatal investigation reported in the literature. Javert and Barton (1952) found a much lower incidence in foetuses aborted at four months.

Nine of the 11 babies had severe associated malformations, and in eight the malformations were multiple. This incidence of 81% is comparable with the 76% found by Benirschke and Brown (1955) and much higher than the incidence of 33% recorded by Hyrtl (1870), and the 56% of Otto (1830). There were malformations of the lower urinary tract in seven babies. One was a sirenoid foetus with no perineal orifices, one had valvular obstruction of the posterior urethra, two had extreme hypoplasia or agenesis of the bladder, and three had atresia or severe stenosis of the bladder neck. In two cases with bladder neck obstruction there was also rectal atresia. There were four cases with renal hypoplasia or agenesis, four cases with malformations of the heart, and two with oesophageal atresia. Ballantyne (1904) stated that the commonest associated malformation was defective development of the bladder and sirenomelia. Benirschke and Brown (1955) found mainly malformations of the heart and central nervous system, while anencephaly was the commonest malformation found by Hyrtl (1870).

There were two monovular twins. In both cases the other twin had two umbilical arteries and no malformations. There was also a high incidence of twinning in Benirschke and Brown's (1955) cases. They found one monovular and four binovular twins, a total incidence of 9%. An abnormal cord was found in each pair. Hyrtl (1870) described female monovular twins (incidence 7%) and male triplets, one foetus in each set having the abnormality. Schatz (1900) found 11 cases in monovular twins and one in a single foetus. In each case only one of the twins had one artery.

There were seven placentas available for examination. One was infarcted and the remainder were normal. One umbilical cord was abnormally long, one was short and a third had a velamentous insertion. Benirschke and Brown (1955) found a high incidence of placental anomalies such as circumvallation, circum-margination, velamentous insertion of the cord and extensive infarction. Ballantyne (1898) stated that the placentas of sympodia tended to show abnormalities of size, shape, consistency and mode of insertion of the cord.

There were equal numbers of live and stillbirths. There was also a high incidence of stillbirths (76%) in Benirschke and Brown's (1955) cases. Hyrtl (1870) found only 7% were stillbirths, but this was probably due to autopsies being infrequently performed on stillbirths.

There were equal numbers of male and female foetuses, and this agrees with the findings of most authors. Kampmeier (1927), however, found a male preponderance in sirenoids, and Hyrtl found only males in his series of 12 single foetuses.

No correlation was found between the abnormality and maternal factors. Of the mothers 60% were multiparous, and their ages ranged from 17 to 25 years. The pregnancies were normal in seven cases, in one there was a threatened abortion, and in one toxaemia of pregnancy. Benirschke and Brown (1955) had found a high incidence of toxaemia and hydramnios.

The condition can be simply diagnosed at birth by careful examination of the cut surface of the umbilical cord. This is of little practical value in the presence of obvious gross malformations. There were no gross external malformations in six of the cases, however: two of these, Cases 10 and 11, showed no associated malformations at autopsy; two, Cases 5 and 7, had malformations incompatible with life; two, Cases 2 and 9, had malformations which may be amenable to surgical treatment. Therefore a newborn infant without gross malformations visible externally, but with only one umbilical

artery, has a 2:1 risk of severe internal malformations, which may warrant early surgical correction.

Summary

Eleven cases of single umbilical artery are described. They were encountered among 411 autopsies on stillborn and live-born babies under 8 weeks of age. Nine had severe associated congenital malformations involving particularly the urinary tract. Absence of an umbilical artery can be diagnosed by simple examination of the cord at birth. In the absence of severe external malformations such an infant has a 2:1 risk of internal malformations which may require early surgical treatment.

REFERENCES

Ballantyne, J. W. (1898). The occurrence of a non-allantoic or vitelline placenta in the human subject. *Trans. Edinb. obstet. Soc.*, 23, 54.
—— (1904). *Manual of Antenatal Pathology and Hygiene*, Vol. 2: The Embryo, p. 592. Green, Edinburgh.
Bauhin, C. (1621). *Theatrum anatomicum*, Lib. 1, cap. 13. Quoted by Hyrtl (1870).
Benirschke, K. and Brown, W. H. (1955). A vascular anomaly of the umbilical cord. *Obstet. Gynec.*, 6, 399.
Browne, F. J. (1925). On the abnormalities of the umbilical cord which may cause antenatal death. *J. Obstet. Gynaec. Brit. Emp.*, 32, 17.
Hendry, D. W. and Kohler, H. G. (1956). Sirenomelia ('Mermaid'). *J. Obstet. Gynaec. Brit. Emp.*, 63, 865.
Hyrtl, J. (1870). *Die Blutgefässe der menschlichen Nachgeburt in normalen und abnormalen Verhältnissen.* Braumüller, Vienna.
Javert, C. T. and Barton, B. (1952). Congenital and acquired lesions of the umbilical cord and spontaneous abortion. *Amer. J. Obstet. Gynec.*, 63, 1065.
Kampmeier, O. F. (1927). On Sireniform Monsters, with a consideration of the causation and the predominance of the male sex among them. *Anat. Rec.*, 34, 365.
Noortwyk, W. (1743). Uteri humani gravidi anatome et historia. Quoted by Hyrtl (1870), p. 48.
Otto, A. W. (1830). *Lehrbuch der pathologischen Anatomie des Menschen und der Thiere.* Rücker, Berlin.
Richart, R. and Benirschke, K. (1958). Gonadal dysgenesis in a newborn infant. *New Engl. J. Med.*, 258, 974.
Schatz, F. (1900). Die Gefässverbindungen der Placentakreisläufe eineiiger Zwillinge, ihre Entwicklung und ihre Folgen. *Arch. Gynäk.*, 60, 81.

THE 'STIFF MAN SYNDROME' IN A BOY

BY

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Tetanus is common in Malaya, and the case to be described, although first diagnosed as recurrent tetanus, is put forward as a case of the 'stiff man syndrome' or progressive fluctuating muscular rigidity and spasm.

Case Report

In October, 1958, a Chinese boy, aged 7 years, was transferred to the Children's Unit with a diagnosis of recurrent tetanus. According to the mother, he had been ill intermittently since 1957 when he was first admitted to hospital complaining of stiffness of the body and inability to open his mouth. He apparently recovered from this illness, but was readmitted on two further occasions with similar complaints. For over one year he had been unable to open his mouth properly. Since August, 1958, this difficulty had increased so that taking solid food was impossible and he had been fed on fluids only. From time to time during the past year his face had 'twisted up' (mother's description). His mother had brought him to hospital again because for the last month he had been 'stiff all over' and had been having 'fits'. She was quite certain that he had never had any injury, and that before 1957 he had been quite well. He had never been immunized. There were five other children in the family, all of them well.

He had been in different hospitals three times. On his first admission in February, 1957, he had complained of trismus and stiffness of the back and abdomen. He was treated as a case of tetanus, although there was no history of injury, and he had no typical tetanic spasms whilst in hospital. He was admitted on two further occasions in April, 1957, and January, 1958. Each time his complaint was difficulty in opening his mouth, but rigidity of the abdominal muscles (they were described as 'board-like') was noted on examination. There was no involvement of the arms and legs, and the child was able to walk. In January, 1958, recurrent left facial spasms were noted for the first time.

On each occasion the stiffness disappeared in about three weeks and he was discharged, although the inability to open his mouth remained. No investigations were carried out, and no firm diagnosis was made.

In summary, therefore, since February, 1957, the child had suffered from a recurrent illness involving stiffness of the abdominal muscles, together with difficulty in opening his mouth. The latter complaint had become permanent and was associated with left facial spasms.

When seen by me in October, 1958, the child was conscious, alert and lying quietly in bed. He lay like a 'wooden soldier' with the head, trunk, arms and legs quite straight. The feet were plantar flexed and the hands were in the mains d'accoucheur position. There was a suggestion of risus sardonicus about the mouth, and the muscles of the neck, chest, abdomen and back were tense, clearly outlined, and appeared to be in a state of permanent contraction. There was no opisthotonus although there was marked neck stiffness due to the rigid neck and trunk muscles. The abnormal appearance and

FIG. 1.—Appearance of child during a spasm.

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feel of the muscles were absent in the legs and in the forearms.

The child was intelligent and cooperative throughout what appeared to be a most painful physical examination. When at rest he was quiet but when examination was attempted there were violent intermittent spasms of the face and neck muscles. Each spasm lasted about 30 seconds, was accompanied by profuse sweating and appeared to be extremely painful. The similarity to tetanus was marked, although the child was emphatic that the spasms were painless. They were precipitated by efforts to talk, to open the mouth, tapping the face, movements of the arms and legs, and by nursing procedures (Fig. 1).

The other muscles of the body, although remaining rigid, were not involved in the spasms. The child could open his mouth 0·5 cm. only (Fig. 2). It was interesting

FIG. 2.—Demonstrating inability of child to open mouth.

to note that the feel of the edge of the masseter muscles, which is so characteristic in tetanus, was absent in this child. Neither was any jaw jerk obtained. The child was unable to sit, turn in bed, or to stand. When he was supported on his feet there was an immediate increase in the rigidity of all muscles, including the limbs, together with the most violent spasms of the face and neck. The muscles of the trunk were hard and unyielding, and the abdomen was board-like. The feet became strongly plantar flexed. The child remained stiff and straight when lifted from the bed (Fig. 3) but could be 'bent' into a sitting position.

Passive movements of the limbs showed some 'lead pipe' rigidity greater in the legs than in the arms. Active movements were carried out slowly, and power and coordination were poor, being limited by the stiffness. There was no weakness nor wasting of any particular

muscle group, and there were no involuntary movements (apart from the spasms), tremors, or muscle fibrillation. The limb reflexes were normal and there were no sensory abnormalities. During sleep the child was relaxed and the muscles were quite soft. Examination of the heart and lungs revealed nothing remarkable.

The child remained in hospital for 30 days during which time the stiffness and rigidity of the muscles slowly regressed, regression being uniform throughout the affected muscles. The spasms became less violent and frequent and there was some improvement in his ability to open his mouth. Two weeks after admission the child was able to walk, but with a wooden stiff-legged gait. If he lost his balance he fell forward completely stiffly. At no time during his stay did he complain of any muscular pain. Apart from a high protein diet enriched with vitamins he received no specific treatment.

At the time of his discharge he was fairly active. There was no stiffness nor tenseness of the muscles. The spasms had ceased and he could open his mouth 1·5 cm. He disliked trying to run because he said his legs felt heavy. Since discharge he has been seen regularly and has remained almost free from symptoms. He is still unable to open his mouth fully and he dislikes running. His mother says that occasionally his face 'twists up'.

FIG. 3.—Demonstrating overall rigidity of child when lifted.

Whilst in hospital he was investigated in detail. Blood biochemistry was normal (Na; K; Ca; CO_2 combining power; inorganic phosphate; plasma proteins; blood urea). A four-hour glucose tolerance test with simultaneous phosphate estimations was normal. Liver function tests were normal, cerebrospinal fluid examination was normal, as was the electrocardiograph. Radiographs of the skull and temporo-mandibular joints showed no lesion to account for his inability to open his mouth. The urine was tested repeatedly for reducing substances but they were absent on all occasions. Muscle biopsy was not performed.

Discussion

For want of a more accurate term the stiff man syndrome has been used to describe this case.

Moersch and Woltman (1956), who first described the condition, labelled it more accurately progressive fluctuating muscular rigidity and spasm. They record having seen 14 cases (all adults) in 32 years. In the case they described in detail there was episodic tightening of the muscles of the neck, which gradually increased in frequency, duration and extent. Four years after the onset of the disease the neck muscles were permanently rigid, as were the muscles of the trunk, abdomen and back. The rigidity was punctuated by moderately painful spasms, which were precipitated by a sudden jar or voluntary movement. Twelve years after the onset of the symptoms he still had the muscle rigidity and the spasms. Of the other 13 cases summarized, stiffness, rigidity or tightness was the chief initial complaint. All cases had experienced spasms, but these were not always painful or marked. Ten of the cases had a gradual onset and the muscles of the neck or trunk and shoulder were first affected. In all cases the stiffness spread to other muscles. Involvement of the hands and feet was minor, and the face was not involved in any case. In no case was there any mental deterioration. The cases were followed up from three to 14 years, and in all except one there was a gradual increase in the disability. All cases were notable for the complete lack of other physical signs, the failure of investigations to reveal any abnormality and the failure of all treatment to influence the course of the disease. Asher (1958) and Price and Allott (1958) describe adult cases of this syndrome. In both cases, however, the descriptions differed from Moersch in that the feet and legs were heavily involved, causing a pronounced talipes equinovarus. In Asher's case there were additional mental changes. Similarly, the present case differed from the description of Moersch in that there was marked involvement of the face, although in other respects the similarity was close.

If this syndrome is to be admitted as an entity, therefore, it seems that any group of muscles may be involved initially and that the course of the disease is subject to wide variations. The only common factor is the fluctuating rigidity, coupled with an almost complete lack of other abnormal findings, and the failure of all forms of treatment.

Clinically the syndrome resembles recurrent tetanus in many ways. True second attacks of tetanus in the same patient are very rare. I have found only two clear references in the literature (Gobus, 1950; Gunaratna, 1958). Westwater (1917) mentions a case, but as the attack followed a gunshot wound, and as it is not clear whether the case had a surgical treatment, this case may be a recrudes-

cence due to the persistence of a foreign body. It is surprising that so few cases of true second attacks of tetanus are on record, since a clinical attack of tetanus does not give any immunity to subsequent attacks (Spaeth, 1949). Professor Adams of Durban states that in a series of 360 cases of tetanus he has not seen any true second attack. Chronic recurrent tetanus due to the persistence of a foreign body or focus of infection in the tissues is relatively well known (Mouchet, 1916; Adams, 1958). The clinical picture of tetanus can vary very widely, with few or many muscle groups involved, and with any degree of hypertonus. The tetanic spasms may be absent or present in any degree of severity.

Nevertheless, the picture of the stiff man syndrome, when viewed as a disease process in time, is quite unlike that of tetanus, and on clinical grounds alone it is reasonable to assume that there is no relation between the two conditions.

It has been suggested (Leading article, 1956) that the stiff man syndrome may be due to degenerative changes in the basal ganglia and that the syndrome is a variant of dystonia musculorum deformans. Superficially there are similarities between dystonia and the stiff man syndrome. Wechsler and Brock (1922) described a variant of dystonia in which the involuntary movements were largely absent and in which muscle rigidity was the predominant disability. In both dystonia and the stiff man syndrome muscle stiffness and rigidity, which slowly spreads, is the presenting disability. The end result of both diseases is associated with deformities. In dystonia, however, involuntary movements are a marked feature of the disease and there are often mental changes (Ford, 1952). However, apart from muscle spasm and stiffness, the two syndromes appear to have little in common. Although the present case has not been followed long enough, all the other reported cases showed no clinical evidence of degenerative brain changes.

I have thought it of interest to report this case since, like the cases reported by others, it does not appear to fit any recognizable condition, and so far the syndrome has been reported only in adults.

Summary

A case of the stiff man syndrome or progressive fluctuating muscular rigidity is described. The condition is briefly reviewed.

REFERENCES

Adams, E. B. (1958). Personal communication.
Asher, R. (1958). A woman with the stiff-man syndrome. *Brit. med. J.*, 1, 265.
Ford, F. R. (1952). *Diseases of the Nervous System in Infancy, Childhood and Adolescence.* Blackwell, Oxford.
Gunaratna, N. P. S. (1958). A case of recurrent tetanus. *J. Lady Ridgeway Hosp. Child.*, 7, 3.

Leading Article (1956). Stiff-man syndromes. *Brit. med. J.*, **2**, 1478.
Moersch, F. P. and Woltman, H. W. (1956). Progressive fluctuating muscular rigidity and spasm ('stiff-man' syndrome): report of a case and some observations in 13 other cases. *Proc. Mayo Clin.*, **31**, 421.
Möbus, L. (1950). Über atypischen und rezidivierenden Tetanus. *Z. Kinderheilk.*, **68**, 427.
Mouchet, A. (1916). Chronic recurrent tetanus. *Med. Press*, n.s. **101**, 28.
Price, T. M. L. and Allott, E. N. (1958). The stiff-man syndrome; preliminary report of a case. *Brit. med. J.*, **1**, 682.
Spaeth, R. (1949). Tetanus immunity. *J. Amer. med. Ass.*, **141**, 238.
Wechsler, I. S. and Brock, S. (1922). Dystonia musculorum deformans, with especial reference to a myostatic form and the occurrence of decerebrate rigidity phenomena. A study of six cases. *Arch. Neurol. Psychiat. (Chicago)*, **8**, 538.
Westwater, A. M. (1917). A case of recurrent tetanus. *Brit. med. J*, **1**, 395.

Addendum.

Since submitting this paper, a case of recurrent tetanus has occurred at this Hospital, under the care of Mr. S. M. Alhady, details of which will be reported later.

GOUT AND
CEREBRAL PALSY IN A THREE-YEAR-OLD BOY

BY

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Gout is very uncommon in children, and its appearance in a patient with cerebral palsy does not appear to have been recorded before.

Case Report

A.W. was born on January 20, 1951, at full term after a normal delivery and weighed 7 lb. 6 oz. He was adopted after medical examination aged 1 week. He was slow to sit up, his muscle tone was poor and at 1 year a diagnosis of cerebral palsy was made. In May, 1953, a ganglionic swelling was removed from his left foot which contained amorphous debris on histological examination. He was then showing signs of athetosis, for which physiotherapy was prescribed, and he was sent to a day school for children with cerebral palsy, which he still attends. In the same year he was admitted to hospital for investigation but developed pneumonia, after which the athetosis became more pronounced. In September, 1954, he developed diffuse painful swellings of the fingers and toes. Radiographs of the hands and feet revealed no abnormality and the sedimentation rate was 9 mm./hr. (Westergren). A diagnosis of Still's disease was made and aspirin prescribed. In 1956 he suffered an exacerbation of his symptoms and in 1958, after a period of absence from school on account of pain and restlessness, he was seen with gross swellings of the fingers and toes. These were lilac in colour and studded with white calcareous deposits. The skin was ulcerated in several places and the appearances were those of gout. His blood uric acid at that time was 10·6 mg.% and he was treated with colchicine $\frac{1}{120}$ gr. four times a day. Ten days later his restlessness was much improved and the lesions were less inflamed, but the dose had to be reduced to $\frac{1}{240}$ gr. on account of diarrhoea. This was later augmented with benemid. Shortly afterwards, as a result of infection entering through one of the ulcerated toes, he developed a large abscess in his right forearm which however healed rapidly after incision but left him emaciated and anaemic. He was transfused on account of iron intolerance and the anaemia did not recur. While in hospital his lower lip became severely ulcerated and six teeth were extracted under general anaesthesia. This in turn led to bronchitis from which he recovered. After a seaside holiday he became much better nourished. On September 19, 1958, he developed a severe generalized convulsion from which he recovered rapidly.

At the present time he is a surprisingly contented child with a high grade mental defect. He can speak with difficulty and can assimilate simple teaching. He is very emaciated, weighing only 25 lb. at 7 years (Fig. 1) and he

FIG. 1.—Showing emaciation and characteristic posture. Note bitten lip.

suffers from severe generalized athetosis with extensor spasms. He can neither sit nor stand unaided, grimacing is frequent, speech and swallowing are impaired and he salivates continually. The gout involves both hands and feet (Figs. 2 and 3) and the lobes of the ears. The digits are red and swollen with numerous white uratic deposits, and although partially controlled by treatment exacerbations are frequent. There has been no evidence of a

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FIG. 2.—Ulcerated gouty lesions of hand.

FIG. 3.—Gout and tophi on foot. Also inflamed ganglion.

return of his anaemia and bone marrow examination shows no evidence of leukaemia.

Other laboratory examinations include: 24-hour uric acid output 504 mg.; blood urea 30 mg.%; Mantoux reaction negative. Radiographs show gouty changes in the hands (Fig. 4) and also subluxation of the right hip. Chromatography of the urine shows no abnormality.

Discussion

Gout is very uncommon in childhood. Bernstein (1947), in an excellent historical review, says that Hippocrates, Sydenham and Heberden never saw it and that Hippocrates believes that it did not occur before puberty.

Sydenham, who developed gout at 25, would certainly have remarked on it had he seen it. The first writer to describe it was Morgagni: '*Ipsi puellas vidi qui infanta vix peracta, acerbis articulorum doloris, prehensi decumbant*'. The next writer is Gairdner (1854), who says that he had seen an infant on the breast who had a strong family history of gout. Still (1927) and Garrod (1876) also make reference to juvenile cases.

In modern writings two types of juvenile gout are recognized, a rare, often fulminating type identical with that seen in adults, and a more common form associated with leukaemia or haemolytic anaemia. A further type associated with chronic liver disease has also been described. The first detailed description in a child is that of Mayer von Schopf (1930) in a baby of 5 weeks. This appears to have been of the adult type although it was associated with an anaemia. Death resulted from broncho-pneumonia. Two cases are recorded at $3\frac{1}{2}$ years, one by Vining and Thompson (1934) in a child with leukaemia, and another by Rauch (1950) with symptoms from 3 years. Apart from these cases all the others were observed after the age of 10. The maximum incidence of gout is in the fifth decade, and it declines in frequency in youth and age. Examples of gout in young persons are described by Claiborne (1940) at 17 years, Bernstein (1947) at 12, 14 and two at 16, Berk (1948) at 11 and Flinchum and Powers (1951) at 15, 26 and 25. Gout and leukaemia in a boy of 11 is recorded by Franck (1944), and anaemia and gout are recorded by

FIG. 4.—Radiograph of hands showing erosions and calcareous deposits.

Nordmann and Höhne (1951) in a child of 12; Morgano and Zino (1953) and Lambie (1940) also report cases. Jeune, Charrat and Bertrand (1957) describe two interesting cases of chronic liver disease associated with a high blood uric acid, one of whom suffered from gout.

No connexion between gout and disease of the central nervous system has been described apart from the degenerative vascular changes which it produces and one case of tophi in the spinal cord causing paraplegia (Koskoff, Morris and Lubic, 1953).

In the present case we believe that the poor general condition of the patient, which resulted from his cerebral palsy, may have aggravated an inherited gouty diathesis and resulted in the premature appearance of symptoms.

Summary

Gout is described in a boy with athetoid cerebral palsy. The disease was first observed at the age of years. No connexion between the two conditions could be established.

The boy remains under the care of Mr. Kenneth Gout, F.R.C.S., and I am much indebted to him for referring him to me and allowing me to publish this report about him.

REFERENCES

Berk, M. E. (1948). Gout—report of an unusual case in a young man. *Amer. J. med. Sci.*, **215**, 290.
Bernstein, S. S. (1947). Gout in early life. *J. Mt Sinai Hosp.*, **14**, 747.
Claiborne, T. S. (1940). Gout in a 17 year old girl. *J. Amer. med. Ass.*, **115**, 38.
Flinchum, D. and Powers, J. A. (1951). Gout in young people. *N.C. med. J.*, **12**, 433.
Franck, G. (1944). Leukose og Arthritis urica. *Nord. Med.*, **21**, 605.
Gairdner, W. (1854). *On Gout, its History, its Causes, and its Cure*, 3rd ed. Churchill, London.
Garrod, A. B. (1876). *Gout and Rheumatic Gout*, 3rd ed. Longmans, Green and Co., London.
Hippocrates, Aphorisms 6, No. 30.
Jeune, M., Charrat, A. and Bertrand, J. (1957). Polycorie hepatique —hyperuricémie et goutte. *Arch. franç. Pédiat.*, **14**, 897.
Koskoff, Y. D., Morris, L.E. and Lubic, L. G. (1953). Paraplegia as a complication of gout. *J. Amer. med. Ass.*, **152**, 37.
Lambie, C. G. (1940). A study of juvenile gout in a patient suffering from chronic erythronoclastic anaemia of obscure origin, together with observations upon the physical state of uric acid in the blood and the effects of splenectomy. *Med. J. Aust.*, **1**, 535.
Mayer von Schopf, E. (1930). Gicht bei einem 5 wochen alten Säugling. *Klin. Wschr.*, **9**, 2148.
Morgano, G. and Zino, F. (1953). Considerazioni su di un caso di gotta giovanile. *Arch. E. Maragliano Pat. Clin.*, **8**, 915.
Nordmann, M. and Höhne, K. H. (1951). Die juvenile Poikilocyten —Anämie mit generalisierter Arthritis urica. *Folia haemat.* (*Lpz.*), **71**, 98.
Rauch, H. W. M. (1950). Gicht bei einem 3½ jährigen Mädchen. *Med. Mschr.*, **4**, 931.
Still, G. F. (1927). *Common Disorders and Diseases of Childhood*. 5th ed. Oxford University Press, London.
Vining, C. W. and Thomson, J. G. (1934). Gout and aleukaemic leukaemia in a boy aged five. *Arch. Dis. Childh.*, **9**, 277.

CALCIFICATION OF THE DIGITAL VESSELS IN A CHILD WITH RHEUMATOID ARTHRITIS

BY

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Calcification of blood vessels occurring during the course of rheumatoid arthritis in a child appears to be unique. It is hoped therefore that this report will be of interest.

Case History

The girl is now 9 years old. Her illness began at the age of 2 years with fever, joint swellings, pericarditis with effusion, rash, splenomegaly, lymphadenopathy and anaemia, indeed the full clinical picture of Still's disease (1897). There was a family history of rheumatic fever on both the paternal and maternal sides but none of rheumatoid arthritis. She was treated along conservative lines in the Royal Hospital for Sick Children, Edinburgh, for one year and then, during her second year there, she was given 20 mg. of A.C.T.H. gel daily for six months followed by 25 mg. of A.C.T.H. gel every second day for six months. Only slight improvement was noted and later it was found that she could be just as well controlled on 50 gr. of aspirin daily. By the time of her discharge home the heart had returned to normal but the joints of all four limbs were still affected and also the cervical spine. She could walk a little with support.

The family moved to Dundee shortly afterwards. One month later, at the age of 4½ years, she was admitted to Dundee Royal Infirmary with a recurrence of pericarditis and widespread acute arthritis. During the ensuing eight months of complete bed-rest, despite such physiotherapy as she could tolerate, the condition of the joints deteriorated. When the pericarditis had resolved, after rather a stormy course with heart failure, the child was transferred to the Children's Orthopaedic Unit so that serial plasters could be made to improve the position of her joints, in which movement was very limited. She was there for five months but again her general condition gave cause for anxiety and she was returned to the paediatric ward.

It was then evident that after three years of active rheumatoid arthritis she had developed amyloid disease. The liver was more than a hand's breadth enlarged and the spleen three fingers' breadths enlarged. There was gross albuminuria (between 600 mg./100 ml. and 1,200 mg./100 ml.) in the 24-hour samples. None of these findings had been present six months previously. No biopsy was taken as neither the skin nor the lymph nodes were involved, but the Congo red test showed 95% fixation of dye by the tissues in one hour. Although the heart was again clinically normal the arthritis had become even more severe. There was marked dilatation of capillaries at the base of the nails. She could not grasp objects with her hands or move them to her mouth and she could not stand or attempt to walk. Her neck was fixed and her back rigid. Her general condition was poor; she was miserable and suffering a great deal of pain. It was therefore decided to try hormone therapy again. Relatively higher dosage was given on this occasion, namely 20 mg. prednisolone daily for four weeks followed by a gradual reduction to 10 mg. daily. The improvement was striking. Within two months she could feed herself and walk slowly on her own. The B.S.R. fell to normal and remained so for the first time since the onset of her illness. Long term therapy had therefore to be considered.

In order that a check might be kept on the osteoporotic effect of hormone therapy, radiographs were taken of the entire skeleton. These showed gross generalized skeletal decalcification with fusion of the inter-articular processes of the cervical spine and collapse of the fourth to the tenth thoracic vertebrae inclusive (Fig. 1). The lumbar vertebrae were normal. Previous films had shown a normal cervical spine at 3 years but early fusion of the inter-articular processes was present at 4½ years when she was first examined radiologically in Dundee. On neither occasion had a radiograph of the thoracic spine been ordered but one film taken at 4½ years showed collapse of the fourth to the seventh thoracic vertebrae at which point the film was cut off. In addition to the generalized skeletal decalcification there was calcification of the digital blood vessels of the hands and feet (Figs. 2 and 3), almost certainly arterial, although arteriography would have been necessary to prove it. A radiograph of the hands two years previously had shown some osteoporosis around the affected joints but no calcification of the digital vessels. By this time the child had been given a total of 1·47 g. of prednisolone. In spite of the vertebral collapse and severe osteoporosis it was decided

FIG. 1.—Radiograph of spine showing osteoporosis and deformity of vertebrae.

FIG. 2.—Radiograph of hands showing calcification of the digital blood vessels.

FIG. 3.—Radiograph of feet showing calcification of the digital blood vessels and the first right metatarsal artery.

to continue hormone therapy in view of the striking clinical improvement obtained.

A calcium balance was then undertaken to see whether the use of methylandrostenediol would increase the retention of body calcium (Fischer and Hastrup, 1954). The results are summarized in Table 1 for the balance period of 30 days. The diet which the child had been taking for some time and which contained a large amount of milk was first analysed and then kept con-

TABLE 1

RETENTION OF BODY CALCIUM AND PHOSPHORUS

| | Average Daily | | | | Percentage Daily Retention |
| | Intake (mg.) | Output | | Retention (mg.) | |
		Urine (mg.)	Stool (mg.)		
Calcium	1,140	27	439	674	59
Phosphorus	993	134	316	543	55

stant. She had not been having vitamin D supplements and none were given during the balance. The calcium balance was carried out for 10 days on 10 mg. of prednisolone daily. On the eleventh day methylandrostenediol, 30 mg. daily, was added and the balance was continued for another 20 days. No change in calcium or phosphorus retention due to the methylandrostenediol was noted. The calcium and phosphorus balances were very strongly positive throughout the whole period. The average calcium retention by children of early school age was reported as 26% of the intake by Holmes (1945). This child was retaining 59% of her calcium intake.

The considerable retention of calcium in spite of continued prednisolone therapy was thought to be due to the process of recalcification of the skeleton brought about by increased exercise. The calcium balance had presumably been negative during the protracted period of bed rest. The biochemical findings at the time of the balance are summarized in Table 2. The only abnormality was a rise in globulin to 4·2 g./100 ml. with a normal albumin of 4·2 g./100 ml. Electrophoresis showed an increase in α_2 and γ globulins consistent with some

activity of the rheumatoid arthritis. The B.S.R. was 18 mm./hour (Westergren) on the same blood sample.

TABLE 2
BIOCHEMICAL FINDINGS

Calcium	= 10·6 mg./100 ml.
Phosphorus	= 3·8 mg./100 ml.
Alkaline phosphatase	= 16 K.A. units/100 ml.
Urea	= 20 mg./100 ml.
Cholesterol	=180 mg./100 ml.
Bilirubin	= 0·5 mg./100 ml.
Sodium	=139 mEq./l.
Potassium	= 4·8 mEq./l.
Chloride	= 99 mEq./l.
Albumin	= 4·2 g./100 ml.
Globulin	= 4·2 g./100 ml.
Total	= 8·4 g./100 ml.

After five months' treatment with prednisolone the child was able to wash and feed herself and walk on her own and so she was allowed to go home. At home she has continued to improve gradually on prednisolone therapy, 10 mg. daily for two years and, more recently, on 7·5 mg. daily. She can now walk a quarter of a mile. During this period the amyloidosis has regressed with much diminution in the size of the liver and spleen and a reduction of the albuminuria to 25 mg./100 ml. in the 24-hour collections. As previously given, the Congo red test in January, 1955 showed 95% fixation of dye by the tissues at the end of one hour. In May, 1956 the fixation was 87%, in December, 1956 it was 75%, in March, 1958 it was 56% and in March, 1959 it was 65%. Recent radiographs show that general recalcification of the skeleton has taken place although it is not yet normally calcified. There is in addition a diminution in the calcification of the digital vessels. At no time has the blood flow to the digits appeared deficient. On the contrary, one persistent sign of activity has been the dilatation of capillaries at the base of the nails. The skin has never shown any thickening suggestive of dermato-myositis, however, and there were no lupus erythematosus cells in the blood samples examined.

The blood pressure is now 130/100 mm. Hg, whereas before A.C.T.H. therapy it was 110/80 mm. Hg. While 20 mg. of prednisolone was being given daily it was 150/120 mm. Hg.

The child's growth has been retarded since the onset of her illness. Even during this last year when she has been in better health than in previous years there has been an increment of ½ in. only in height. The height of 43 in. at 9 years is well below the third percentile and the weight of 47 lb. is at the third percentile. Her weight has been kept reasonable by slight dietetic restriction. The bone age, judged by the maturation of the skeleton as a whole, is 13 years, i.e. four years in advance, and menstruation occurred abnormally early at the age of 8 years. Pubic hair is present but no axillary hair has appeared. There is early breast enlargement (Fig. 4).
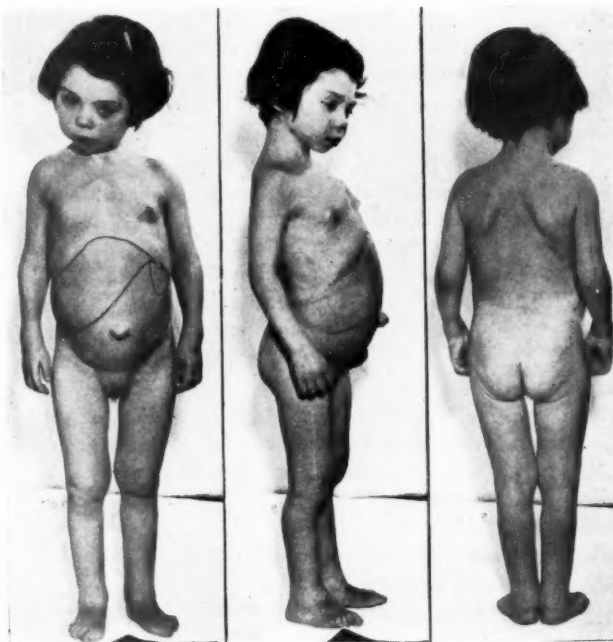
FIG. 4.—Patient aged 9 years.

To summarize, this child has suffered from active rheumatoid arthritis for seven years. During the course of her illness pericarditis has occurred twice. She has developed amyloidosis and gross decalcification of the skeleton with vertebral collapse and calcification of the digital vessels. Prednisolone therapy, even at a late stage, led to a marked improvement in her condition.

Discussion

It is interesting that prednisolone therapy produced so much improvement in this child after four years of severe rheumatoid arthritis, when A.C.T.H. gel, admittedly in relatively smaller dosage, was ineffective in the early stages. The hypertension is probably due to prednisolone but it should be noted that the blood pressure tended to be high even before A.C.T.H. was first given. Early menstruation may also be the result of hormone therapy. Stunting of growth due to the disease would be expected but may have been accentuated by prednisolone. The disparity between the stunting and the advanced bone age is difficult to explain, although the advanced bone age and early menstruation may be related pituitary effects. Amyloidosis is a rare, although recognized, complication of rheumatoid arthritis in childhood. Its regression with improvement in the rheumatoid condition has been described by Parkins and Bywaters (1959).

The vertebral collapse was first noted at the age of 4½ years following one year's treatment with

A.C.T.H. in very moderate dosage. It is unfortunate that radiographs were not taken immediately before prednisolone therapy was begun because in retrospect it is not possible to separate the possible effect of the hormone from that of immobilization in producing generalized decalcification of the skeleton and concomitant calcification of the digital vessels. No other tissues appear to be involved in the process of metastatic calcification. I think that the severe decalcification was chiefly due to prolonged bed-rest with almost complete immobilization of the joints due to rheumatoid arthritis and possibly not at all to A.C.T.H. or prednisolone therapy in view of the small to moderate dosage employed (Welch and Forsyth, 1953; Luder, 1954). This view is substantiated by the finding of a strongly positive calcium balance in the month in which the radiographs were taken and by the gradual recalcification of the skeleton which followed during the next three years of continuous prednisolone therapy. Along with this improvement in skeletal calcification it is of interest to note the diminution in calcification of the digital vessels.

Regarding the aetiology of the calcification of the digital vessels, several possibilities must be considered.

Although amyloidosis affects blood vessels, calcification of the deposits in the vessel walls does not occur.

Calcification of peripheral vessels has been described in a few children with severe chronic renal disease, e.g. hydronephrosis, polycystic kidneys, chronic glomerulo-nephritis, aplastic kidneys or renal tubular disease (Stryker, 1946; Andersen and Schlesinger, 1942; Cochrane and Bowden, 1954). Secondary hyperparathyroidism is ruled out as a cause of metastatic calcification in this patient because of the normal serum calcium and phosphorus levels and the normal blood urea despite amyloidosis of the kidney.

In infants, calcification of the coronary arteries with death from heart failure has been described by several authors (Baggenstoss and Keith, 1941; Andersen and Schlesinger, 1942; Stryker, 1946; Cochrane and Bowden, 1954; Hunt and Leys, 1957). The aetiology of the calcification in these cases was unknown and, although some of the large arteries were involved occasionally in addition to the coronaries, the digital vessels were not affected.

The rare condition of pseudoxanthoma elasticum, if widely disseminated, may be associated with calcification of the vessels due to an infiltration of the degenerated elastic tissue by calcium phosphate. This child, however, did not show the skin discolouration or eye changes associated with this disease. Neither did she have the skin changes of dermatomyositis which may be associated with subcutaneous deposits of calcium.

Vascular calcification in children has been described in hypervitaminosis D and also in severe forms of idiopathic hypercalcaemia (Schlesinger, Butler and Black, 1956; Rhaney and Mitchell, 1956). In retrospect, idiopathic hypercalcaemia was probably present in a similar case described by Lightwood (1932). In these conditions osteosclerosis occurs. Moreover there is no record of the present child having received extra vitamin D.

It is well known that hormone therapy may lead to osteoporosis and that in Cushing's syndrome renal calculi may form. However, no reference has been found to digital vessel calcification due to hormone therapy.

Acute and subacute forms of arteritis associated with rheumatoid arthritis have been discussed recently in the literature (Levin, Rivo, Scott, Figueroa, Fred and Barrett, 1953; Cruickshank, 1954; Kemper, Baggenstoss and Slocumb, 1957), but no mention has been made of calcification of the affected vessels.

Immobilization by bed-rest and particularly total immobilization in severe joint disease causes marked skeletal decalcification. Hypercalcaemia with renal calculi formation may follow but calcification of vessels has not been noted in the literature from this cause.

One cannot therefore be dogmatic regarding the aetiology of the digital vessel calcification in this child. It seems most likely, however, that prolonged immobilization led to decalcification of the skeleton with liberation of calcium which became deposited in digital vessels possibly damaged by rheumatoid disease.

Summary

A girl crippled by rheumatoid arthritis, complicated by amyloid disease, was found to have calcification of the digital vessels in association with widespread decalcification of the skeleton. After prednisolone therapy she was able to walk again. In the next three years considerable recalcification of the skeleton occurred with some diminution in the calcification of the digital vessels and marked regression in the amyloid disease.

REFERENCES

Andersen, D. H. and Schlesinger, E. R. (1942). Renal hyper-parathyroidism with calcification of the arteries in infancy. *Amer. J. Dis. Child.*, **63**, 102.

Baggenstoss, A. H., and Keith, H. M. (1941). Calcification of the arteries of an infant. *J. Pediat.*, **18**, 95.

Cochrane, W. A. and Bowden, D. H. (1954). Calcification of the arteries in infancy and childhood. *Pediatrics*, **14**, 222.

Cruickshank, B. (1954). The arteritis of rheumatoid arthritis. *Ann. rheum. Dis.*, **13**, 136.

Fischer, F. and Hastrup, B. (1954). Cortisone and calcium balance (effect of calcium, vitamin D and methylandrostenediol). *Acta endocr. (Kbh.)*, **16**, 141.

Holmes, J. O. (1945). The requirement for calcium during growth. *Nutr. Abstr. Rev.*, **14**, 597.

Hunt, A. C. and Leys, D. G. (1957). Generalized arterial calcification of infancy. *Brit. med. J.*, **1**, 385.

Kemper, J. W., Baggenstoss, A. H. and Slocumb, C. H. (1957). The relationship of therapy with cortisone to the incidence of vascular lesions in rheumatoid arthritis. *Ann. intern. Med.*, **46**, 831.

Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L. and Barrett, T. F. (1953). The prolonged treatment of rheumatoid arthritis with cortisone and corticotropin. *Amer. J. Med.*, **14**, 265.

Lightwood, R. (1932). A case of dwarfism and calcinosis associated with widespread arterial degeneration. *Arch. Dis. Childh.*, **7**, 193.

Luder, J. (1954). Vertebral collapse after cortisone therapy. *Gt. Ormond Str. J.*, No. 7, p. 15.

Parkins, R. A. and Bywaters, E. G. L. (1959). Regression of amy-loidosis secondary to rheumatoid arthritis. *Brit. med. J.*, **1**, 536.

Rhaney, K. and Mitchell, R. G. (1956). Idiopathic hypercalcaemia of infants. *Lancet*, **1**, 1028.

Schlesinger, B. E., Butler, N. R. and Black, J. A. (1956). Severe type of infantile hypercalcaemia. *Brit. med. J.*, **1**, 127.

Still, G. F. (1897). On a form of chronic joint disease in children. *Med. Chir. Trans.*, **80**, 47.

Stryker, W. A. (1946). Arterial calcification in infancy with special reference to the coronary arteries. *Amer. J. Path.*, **22**, 1007.

Welch, R. G. and Forsyth, C. C. (1953). Still's disease treated with A.C.T.H. and cortisone. *Gt Ormond Str. J.*, No. 5, p. 1.

8

BILATERAL TRIGGER THUMB IN INFANTS

BY

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'Trigger thumb' or 'snapping thumb' in infants is a curious digital restriction in the very young and perhaps is best referred to as a tendovaginitis stenosans of the sheath of the flexor hallucis longus muscle as it is found in infants. The characteristic feature of this condition is the sudden overcoming of involuntary resistance occurring in the normal range of movement of the interphalangeal joint of the thumb, after which movement is again free. Sometimes the sudden overcoming of the resistance is accompanied by a snap. When the physician first sees the infant the interphalangeal joint of the thumb is usually actively inextensible beyond an angle of about 150°. Frequently flexion from full extension is blocked at a slightly more obtuse angle in the same child but the resistance is more readily overcome voluntarily by the stronger flexor tendon.

The recognition of this entity has been mentioned in one or two American text-books of orthopaedic surgery and it has been written about in the continental European literature but there is scarcely a mention of it in the British medical press other than two case reports of the bilateral condition by Rose (1946) in Australia. For this reason a case of bilateral trigger thumb in an infant of 14 months is submitted. Also, it clearly fixes the manner and time of its clinical appearance.

Case Report

T.S. was just 14 months old when her father, who was fond of playing with his young children, noticed for the first time that her left thumb seemed fixed in flexion ('bent at the knuckle'). He believed that had this persistent digital flexion been present earlier he would have observed it. No other member of the family group, in which there were five adults (including two grandparents), had seen or remarked upon the state of the thumb. The father, therefore, was inclined to believe that the limitation of movement had come on suddenly. At the time of his initial observation he immediately compared the two thumbs but the active and passive ranges of movement of the other thumb were normal as far as he could make out.

When the parent brought the infant for advice it was noted that the affected thumb's interphalangeal joint could not extend beyond about 135°, to which angle both active and passive movements were painless. Forced passive extension to the maximal normal limit was sudden and painful enough to make the infant cry. Soon after, within five minutes of the forced passive extension, the joint spontaneously resumed its position of persistent restricted extension. Palpable over the flexor pollicis longus tendon and at the head of the first metacarpal was a lentil-sized nodule in the subcutaneous tissue. The diagnosis was straightforward. However, no comparable nodule in the other thumb was noted at the time. An open operation to split the tendon-sheath only was successful and the skin sutures were removed eight days later. At this time comparison again of the two thumbs showed no functional difference; but 10 days after the removal of the sutures, or 18 days after the operation, the observant father saw with interest and some little distress that an identical limitation of extension of the other thumb had taken place.

Review of the Literature

In 1933 Compere collected notices of 40 cases of trigger thumb and established its rarity in infancy. His collection included bilateral cases in adults and these were comparatively frequent. There were only two reports of cases in children. His case of bilateral snapping thumb came to him when she was 20 years old and she was able to recall that she had had the condition without any real disability resulting since the age of 4 years. His other case he saw when the baby was 9 months old but the mother informed him that both thumbs snapped into extension soon after birth.

Compere (1933) quotes Hauck reporting an infant girl with bilateral involvement. So up to the time of Compere's article only three instances of bilateral trigger thumb appear to have been reported, of which two were in the infant age group. Lipscomb (1944) reviewed 190 cases of tendovaginitis stenosans and found among them only 11 of the thumb, none of these unilateral and none in children. In 1936 Jahss made a point of the fact that because of the rarity of trigger thumb in infants he had not had a

case referred to him for treatment that had been correctly diagnosed. Most of the diagnoses made had been 'congenital contracture of the thumb'. He reported nine cases. None of the mothers of his cases could recall exactly how long the condition had been present in her child. Jahss states that he actually saw 15 cases but confirmed only 10 by operation and their ages ranged from $3\frac{1}{2}$ months to 15 years. Three were bilateral and their ages 15, 2 and $1\frac{1}{2}$ years when he saw them. In 1946 Rose in Australia published two more instances of trigger thumb in both hands, the ages of the infants being 9 months and 2 years respectively. Sprecher (1949) in America reported 12 cases, in none of whom was there an audible snap. In four, locking of the thumb had been noticed immediately or soon after birth, and in the others before the age of 3 years. In three of Sprecher's cases both thumbs were affected and in two cases with one thumb showing the limitation the other thumb was functioning normally although a palpable nodule was present in the tendon. Sprecher refers to Beck who reported six cases but no details are given. Zadek (1942) also described two unilateral cases in whom there was symptomless thickening on the tendon of the other thumb. In 1953 White and Jensen discussed a series of nine cases of trigger thumb, whose ages ranged from 15 months to 6 years. Two cases had a family history and five patients came from the same island in the Hawaiian Group. All cases were unilateral. It was in 1953 also that Chiari was able to give the results of his own method of a subcutaneous operative approach to the stenosed part of the tendon sheath in 100 children. Although Chiari admits to the stenosis being found for the first time in later infancy and childhood, he nevertheless rather unhappily uses the term congenital contracture of the thumb (angeborenen Daumenkontraktur). There is no doubt from his article that his 100 cases were all stenosing tendovaginitis. His contribution would have had an added value if Chiari had analysed his remarkable series into age groups, sex, time of onset, whether uni- or bilateral and so on. It is to be hoped that he will do so. That Chiari was able from his own practice to collect 100 cases on whom to apply his surgical technique suggests the probability that there were others differently treated and that in his part of the world trigger thumb is not so rare an entity as we are inclined to regard it.

Discussion

I have been able to collect nine undoubted cases of bilateral trigger thumb in infants from my review of the available literature. About 25% of the cases

manifesting trigger thumb in infancy have been bilateral. When one attempts an aetiological hypothesis which excludes trauma, *the* causative factor for trigger thumb in adults, one inclines to wonder why it is that many more, if not all cases, do not sooner or later become bilateral. Perhaps closer follow-up observation of unilateral trigger thumb is desirable. Despite Chiari's big series which leaves an impression that tendovaginitis stenosans is not uncommon, all available evidence emphasizes the rarity of the bilateral state.

Clinical recognition of the stenosed sheath of the long flexor tendon of the thumb in infants is made by the fact that there is a persistent, painless limitation of extension of the digit to an angle of about 150°. Passive attempts to extend the interphalangeal joint fully are somewhat painful but possible and sudden, when a snap may be heard. Once the joint is fully extended passive flexion is neither painful nor will it produce a snap. Some parents have given a history of a gradual increase of resistance to full extension and the production of the trigger thumb effect, and eventually a complete locking of the joint at a definite angle. The thumb, when first seen in the locked state or when no attempt has been made passively to overcome the resistance to extension, has been confused with a true congenital contracture of the thumb. In this latter disability, however, there is hyperextension of the metacarpophalangeal joint and flexion of the interphalangeal joint, both of which are fixed. Compere mentions rheumatism, neuritis, periostitis, tenosynovitis, tuberculous osteitis, and recurring dislocation at the interphalangeal joint as some of the mistaken diagnoses in his experience.

Whereas trigger thumb in adults is of fairly frequent occurrence and can usually be associated with a story of preceding repeated minor trauma, bilateral trigger thumb in adults is rare and unrelated to infancy. In infants there has been no history forthcoming of any sort of trauma excepting one case of Zadek's in which there had been definite injury to the thumb so that it was treated at first as a traumatic dislocation and only later did an antecedent trigger thumb show up. In my case the onset of the bilateral manifestation could be looked on as a simultaneous happening.

The stronger pull of the flexor tendon keeps the nodule on the proximal side of the stenosis, the primary pathology being in the tendon sheath, and Zadek regards the tendon thickening as a reaction to pressure on the tendon by the stenosing band. In one case he states that the tendon was oedematous. Jahss described a pathological study of the sheath in which there were hyalinized connec-

tive tissue and fibrous villi but there were no adhesions and no free fluid.

Because trigger finger and trigger thumb in adults can almost always be associated with trauma, Compere postulates that in infants there is a predisposing factor and he proposes that it is the acuteness of the angular change of course and pull of the flexor pollicis longus tendon at the metacarpophalangeal joint; but if this were the factor or even a factor it has been stated that the condition would be much more common, certainly in its bilateral form. It has also been postulated that a congenital anomaly of muscle insertion initiates the condition in the foetus which might account for those cases discovered at or soon after birth. The lateral head of the flexor pollicis brevis muscle and the adductor pollicis muscle have been incriminated. Possible additional bands between these two muscles and passing over the tendon sheath of the long flexor, or an abnormally close relationship between these three muscles may be extra factors, but surgical enquiry has not supported these ideas. And yet a variation of the short flexor muscle of the thumb has been described in which a part of the muscle may be inserted separately into the ulnar side of the proximal phalanx of the thumb with the adductor muscle, when it is known as the first volar interosseous muscle. To reach this point of insertion the shorter muscle would have to cross the long flexor tendon of the thumb.

Sprecher sectioned a piece of the involved part of the tendon and reported evidence of trauma indicated by numerous lymphocytes and monocytes in the stroma of the tendinous tissue. So Sprecher believes that the child's tendency to grasp its thumb into its palm produces a sharp kinking of the tendon over its ligamentous attachment to the bone and that this is enough to provide the necessary trauma. He was also of the opinion that because the newborn infant will grasp its thumb in this way it could hold it in the same way *in utero.*

Whether any ethnic influence plays a role is unknown, but a hint of some such possible factor has been put out by White and Jensen who recorded a family history in two of their cases and five others of Filipino ancestry who came from one island in the South Pacific. Chiari's series was collected in Germany. My case came of allegedly pure Germanic and Sicilian stock.

Summary

An account is given of a curious affection of the sheath of the long flexor tendon of the thumb in infants. Although the incidence of the unilateral condition is by nearly all reports rather uncommon, that of the bilateral state is a rarity. It goes colloquially by the names of 'trigger thumb' or 'snapping thumb' but is perhaps better described terminologically as tendovaginitis stenosans. A report of a case is followed by a review of the literature and a discussion of possible aetiological factors in its development.

REFERENCES

Chiari, K. (1953). Subkutane Sehnenscheidenspaltung zur Behandlung der angeborenen Daumenkontraktur. *Zbl. Chir.,* **78,** 101.
Compere, E. L. (1933). Bilateral snapping thumbs. *Ann. Surg.,* **97,** 773.
Jahss, S. H. (1936). Trigger finger in children. *J. Amer. med. Ass.,* **107,** 1463.
Lipscomb, P. R. (1944). Chronic nonspecific tenosynovitis and peritendinitis. *Surg. Clin. N. Amer.,* **24,** August, p. 780.
Rose, T. F. (1946). Bilateral trigger thumb in infants. *Med. J. Aust.,* **1,** 18.
Sprecher, E. E. (1949). Trigger thumb in infants. *J. Bone Jt Surg.,* **31A,** 672.
White, J. W. and Jensen, W. E. (1953). Trigger thumb in infants. *A.M.A. Amer. J. Dis. Child.,* **85,** 141.
Zadek, I. (1942). Stenosing tenovaginitis of the thumb in infants. *J. Bone Jt Surg.,* **24,** 326.

PAROXYSMAL TACHYCARDIA IN A CHILD SHOWING STOKES-ADAM AND WOLFF-PARKINSON-WHITE SYNDROMES

BY

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Paroxysmal tachycardia in infancy may be accompanied, as in the adult, by some disturbance giving rise to pallor, restlessness, dyspnoea, weakness and usually cardiac insufficiency and decompensation. A labile autonomic nervous system makes infants particularly vulnerable to paroxysmal forms of tachycardia. Exactly what it is that starts this disorder or rhythm is frequently obscure and consequently functional autonomic disturbances must often be assumed to be responsible.

The Stokes-Adam syndrome seen in adults in the course of the development of complete heart block is not often seen in children and the case described below, occurring in a child of 2 years during an attack of supra-ventricular paroxysmal tachycardia, is of unusual interest. The symptoms of cardiac insufficiency, more commonly seen in such cases, were conspicuous by their absence in this instance.

Case Report

A boy (P), aged 2 years and 3 months, was admitted to the Lady Ridgeway Hospital for Children, Colombo, at 9 a.m. on January 14 with a history of 10 to 15 'fits' a day. He had had two fits in the out-patients' department while awaiting admission, each fit lasting one to two minutes. The previous history was that the child was healthy after a normal delivery. There was no illness of any importance before these fits. He had had similar fits when 8 months old for four days, each fit lasting about a minute, and there were four to five fits each day. A similar attack of fits occurred three months later when the child was admitted to this hospital for a few days. He was discharged and had been admitted again subsequently to this hospital and to a branch hospital at Ragama. Each time he was discharged after a few days with a diagnosis of fits due to round worms and, on one occasion, epilepsy. The mother stated that the fits were not associated with any fever. The child became semiconscious for a few seconds before the fit, and appeared to be quite normal afterwards.

On examination at about 9.30 a.m. the child appeared to be a healthy well-fed boy weighing 22 lb. (9·98 kg.).

There were slight pulsations over the veins in the neck. The heart was within normal limits and there were no murmurs. The rate was very rapid—about 220 per minute—and the pulse was regular and very small in volume and tension. There was no cyanosis nor dyspnoea and the child was seated on the bed.

The skin turgor was normal and the fontanelles were closed. There was no spasticity of the limbs or neck. The cranial nerves were normal. The abdomen was soft and there were no masses palpable. The liver and spleen were not palpable. While this examination was going on the child quite suddenly became very pale and fell back on the bed in a faint. He remained so for about 30 seconds. He next had a convulsive fit involving both limbs, lasting about one and a half minutes, and soon regained consciousness; he then appeared to be quite normal in colour and behaviour. It was noticed that during the faint there were missed beats and the heart rate was very slow, about 60 to 64 per minute. The child sat up in bed a few minutes later and seemed to be quite normal and unconcerned with what had happened a few minutes earlier. The heart rate was now very rapid and rose to 140 and later 200 per minute. An electrocardiogram was taken soon after and proved very interesting, as the child had a similar faint and fit while this record was being taken. In fact the record was interrupted during the fit for a minute or so. The recording proved an interesting study. Fig. 1 shows a paroxysmal tachycardia of the supra-ventricular type at a very rapid rate of 260-270 per minute. There are short periods of complete cardiac-standstill varying from 0·6 to 0·8 sec. It was noticed that the child fainted off during this period of asystole and when he recovered a few moments later the rhythm was slow and irregular at first but later was quite regular and rapid and soon reached a rate of 240 per minute. While the E.C.G. was being examined the child had a similar faint and fit and appeared to be quite normal soon after the fit. He was treated with a sedative syrup of chloral (gr. 3 in 1 drachm) 6-hourly and Tab. Digoxin 0·25 mg. 4-hourly from 10 a.m. The pulse rate continued to be over 200 for 24 hours, but 12 hours later it slowed down as shown in the table.

The child continued to have fainting attacks and short

BEFORE FIT

L. I   L. II   L. III

DURING FAINT   L. I.   FIT   SOON AFTER FIT
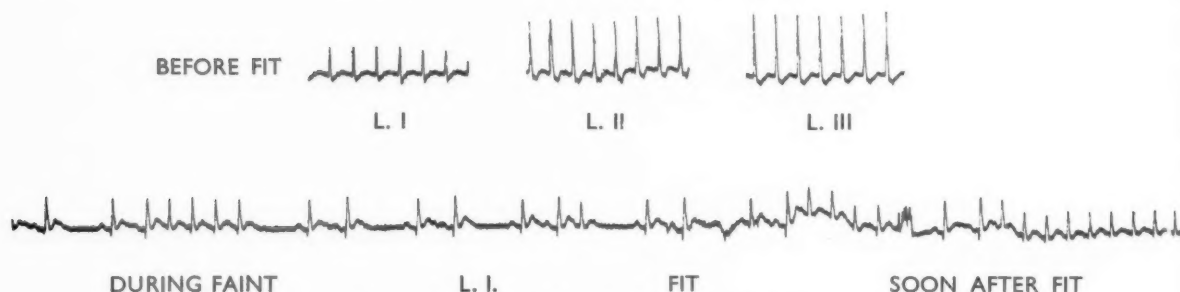
FIG. 1.—Paroxysmal tachycardia of supra-ventricular type.

WOLFF-PARKINSON-WHITE SYNDROME

L. I

L. II   L. III
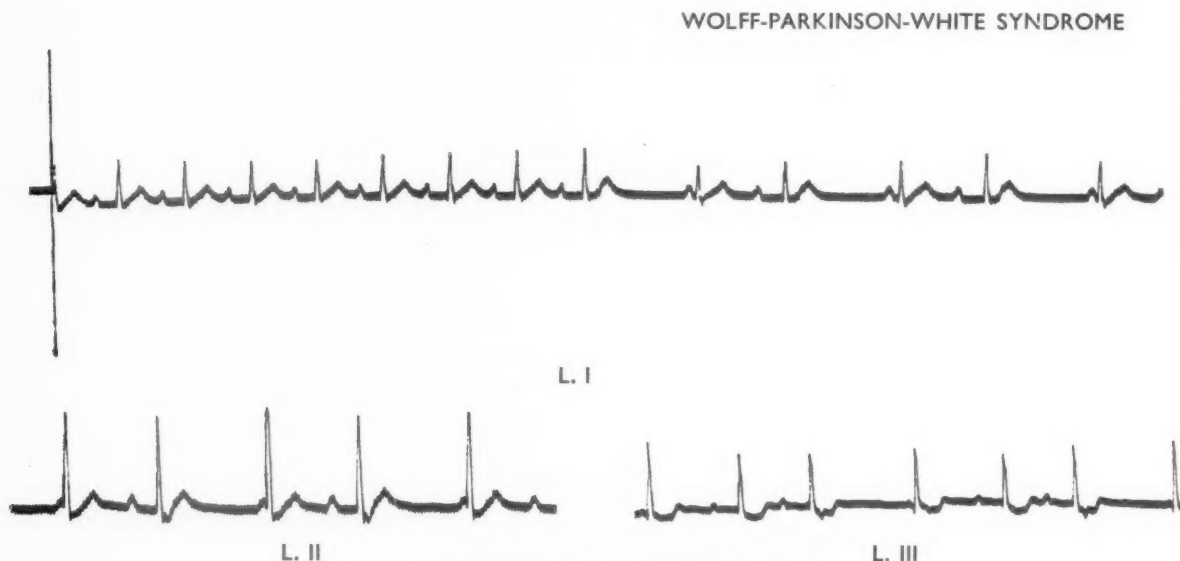
FIG. 2.—E.C.G. taken after discontinuing Digoxin.

fits about three or four times during this period but was generally comfortable and playing in bed.

On January 17, after discontinuing the Digoxin, another electrocardiogram was taken (Fig. 2). It is seen that Lead 1 starts off with eight normal beats but the ninth is absent while the PR interval of the tenth beat is 0·08 sec. This part of the record shows that every

second or third beat has a short PR interval and that each of these beats is preceded by a dropped beat. The shortened PR interval varies from 0·02-0·08 sec. (the normal in infants being not less than 0·12 sec.). The QRS complex is widened 0·11 sec. with slurring of the upstroke of the R wave (the normal in infancy being 0·05 to 0·06 sec.). There are therefore on this record complexes of the Wolff-Parkinson-White syndrome type, each being preceded by a dropped beat. The slurring and widening of the QRS complex with short P waves indicates the presence of the Wolff-Parkinson-White syndrome without any doubt. The E.C.G. records on January 23 (Fig. 3) and February 17 (Fig. 4) showed a

TABLE

		Treatment	Pulse Rate/min.
January 14	10 a.m. ..	0·25 mg. Digoxin	240
	4 p.m. ..	,,	240
	7 p.m. ..	,,	240
	11 p.m. ..	,,	240
January 15	3 a.m. ..	,,	230
	10 a.m. ..	,,	220
	2 p.m. ..	,,	220
	6 p.m. ..	,,	210
	10 p.m. ..	,,	120
January 16	6 a.m. ..	,,	160
	10 a.m. ..	,,	140
	2 p.m. ..	,,	136
	6 p.m. ..	,,	108
	10 p.m. ..	,,	112
January 17	6 a.m. ..	,,	120

L. I   L. II   L. III
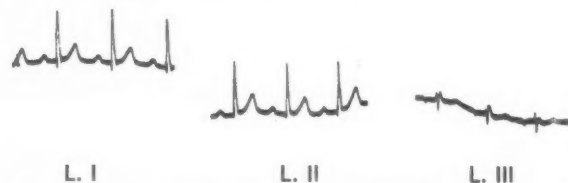
FIG. 3.—E.C.G. showing normal picture with normal rhythm one week later.

L. I   L. II   L. III

AVR   AVL   AVF
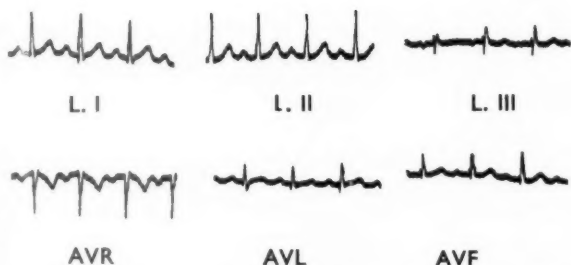
Fɪɢ. 4.—E.C.G. showing normal picture with normal rhythm one month later.

normal picture with normal rhythm. On January 26 the child had two short fainting attacks without any convulsions and Digoxin was given again for four days. The child had another faint on February 2 and on February 17, after being quite well and happy, he left us. A follow-up two years later showed the child to be in good health, with a heart normal in rhythm and rate.

Comment

The case recorded is that of a 2-year-old child who had a paroxysmal tachycardia of the supra-ventricular type and showed fainting attacks followed by fits very similar to the Stokes-Adam syndrome seen in adults with heart block. A further interesting feature was that on recovering the child showed the presence of the Wolff-Parkinson-White syndrome in the electrocardiogram. This latter syndrome is an electrocardiographic entity and has been the subject of much discussion and study since it was originally described by Wolff, Parkinson and White (1930). Gleckler and Lay (1952) have described the Wolff-Parkinson-White syndrome in a 4-month-old infant with paroxysmal tachycardia in whom an electrocardiogram made on cessation of the arrhythmia showed the presence of the syndrome. The interest in this case is that, besides the Wolff-Parkinson-White syndrome, this child also showed the presence of Stokes-Adam while in hospital.

REFERENCES

Gleckler, W. J. and Lay, J. V. M. (1952). Wolff-Parkinson-White syndrome and paroxysmal tachycardia in infancy. Report of a case. *J. Amer. med. Ass.*, **150**, 683.
Wolff, L., Parkinson, J. and White, P. D. (1930). Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. *Amer. Heart J.*, **5**, 685.

SPONTANEOUS HAEMORRHAGE
FROM THE INTERNAL CAROTID ARTERY IN A CHILD

BY

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The case described below shows a child in whom there was a spontaneous haemorrhage from the internal carotid artery in relation to a para-pharyngeal abscess.

Case Report

A boy aged 7 was admitted to hospital after having vomited a small quantity of blood on two occasions during the preceding day without warning or preceding nausea. For six days he had been ill with a sore throat, lassitude and malaise, while the left side of his face and neck had developed a swelling which suggested a diagnosis of mumps.

The boy was pale and inert. He showed a mild pyrexia (100·2° F.) while his pulse was 120 per minute and blood pressure 120/80. A red swelling was visible in the left wall of the pharynx but its extent was not defined as trismus limited inspection. The lymph nodes along the left jugular vein were enlarged.

Three hours after admission a copious haemorrhage occurred. An observer related that the child neither coughed nor vomited but that the blood seemed to well up from the throat.

An immediate operation was deemed necessary and performed by Mr. R. S. Lewis. Under anaesthesia the swelling in the left of the pharynx was confirmed and found to extend from the level of the soft palate down to the epiglottis. The overlying mucous membrane was not discoloured by ecchymosis or inflammation. It bore a ragged opening below and behind the left tonsil leading into a cavity containing blood clot.

An incision was made along the anterior border of the left sternomastoid muscle; the soft tissues were indurated and stiffened while the exposure of the left external carotid artery was impeded by enlarged lymph nodes. The short length of external carotid artery exposed allowed ligature below the origin of the superior thyroid artery.

During the ensuing night a small haemorrhage occurred, but for the next 36 hours the child improved and there was no bleeding until suddenly two days after operation this boy, without warning, lost two or three pints of blood in a cascade from his mouth in three minutes, quickly becoming unconscious, pale and pulseless.

A blood transfusion was started and the child was taken to theatre where the wound was re-opened and the left common carotid artery was divided between ligatures. Three pints of blood were transfused.

Next morning the boy was sitting up in bed cutting paper flags although examination showed signs of a mild right hemiplegia with slight weakness in the right limbs, an accentuated right ankle jerk and extensor plantar response.

During the next 12 hours the child slowly lost consciousness and remained in coma for 48 hours. To preserve the cerebral circulation from spasm and thrombosis Priscol and heparin were given and both stellate ganglia were injected with Xylocain (1·5 ml. of a 2% solution).

Recovery of his mental state was gradual. For the next five days he was half conscious and when discharged two weeks later he was fully conscious but showed an emotional lability and lack of concentration. The only neurological sign was slight right facial weakness.

Later reports of his schooling show that, although showing imagination, he was backward at first through lack of reasoning power, but that he has now caught up with his fellows.

Discussion

The severity of the haemorrhages, especially the last, showed that a major artery was involved. That bleeding recurred after ligation of the external carotid artery and was controlled by ligature and division of the common carotid artery showed that the bleeding vessel was the internal carotid artery. The section of the common carotid artery removed the sympathetic supply to the distal part, preventing spasm and minimizing ischaemic changes in the brain (Rogers, 1947). Although knowledge of the site of bleeding would have suggested the common carotid artery for ligature in the first instance, it is doubtful if this alone would have arrested the haemorrhage in view of the free collateral circulation through the branches of the external carotid artery.

This case is notable in having by the two ligatures

efected complete arrest of blood flow into the left internal carotid artery with little, if any, permanent change in the brain. In the recorded cases (Wood, 1953) 30% of such cases ended fatally or showed brain damage.

Finally this case stresses the nearness of the internal carotid artery to the pharynx. It may lie as little as 2 mm. below the mucous membrane.

Recent literature shows few cases in which a carotid artery was ligated for spontaneous rupture of the internal carotid artery; one was described by Woodruff in 1945 and one by Beck in 1947.

On the other hand, Salinger in 1934 described over 200 cases of abscess in relation to the pharynx, of which 13 required ligation of one carotid artery.

We thank Mr. R. S. Lewis and Dr. Mary Wilmers for permission to publish this case.

REFERENCES

Beck, August L. (1947). Deep neck infection. *Ann. Otol. (St. Louis)*, **56**, 439.
Rogers, Lambert (1947). Ligature of arteries, with particular reference to carotid occlusion and the circle of Willis. *Brit. J. Surg.*, **35**, 43.
Salinger, Samuel (1934). Hemorrhage from pharyngeal and peritonsillar abscess. *Laryngoscope (St. Louis)*, **44**, 765.
Wood, Golding P. H. (1953). Ligation of the carotid vessels. *J. Laryng.*, **67**, 284.
Woodruff, George H. (1945). Massive pharyngeal hemorrhages. *Ann. Otol. (St. Louis)*, **54**, 202.

BLOOD URIC ACID LEVELS IN MOTHERS AND INFANTS AT BIRTH

BY

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This study has been undertaken to determine a pattern of blood uric acid levels in normal mothers and their full-term infants at the time of birth. Blood samples were taken from the umbilical vein to determine the infant levels and from the maternal venous blood at the time of delivery to estimate the mothers' blood uric acid levels. The uric acid estimations were done by the method of Folin and Trimble (1924). Table 1 summarizes the findings of this study.

Steenstrup (1956) has discussed hypo-uricaemia occurring during pregnancy and, in an extensive study of plasma uric acid levels in 280 cases, he found a moderate hypo-uricaemia to be present during the greater part of normal pregnancy. He used the method of Praetorius and Poulsen (1953) for estimating his uric acid levels. Crawford (1939) found a rise in plasma uric acid levels during labour and a fall in the early puerperium so that normal values were reached by the third day after delivery. The height of the rise during labour appeared to depend on the length of labour. Benedict's (1922) colorimetric method was used for these estimations.

In the present study the maternal ages of the 21 cases ranged from 18 to 41 years and their parity included seven primigravidae, nine with one previous pregnancy and the remainder having had from two to 10 previous infants. The 21 infants included eight males and 13 females. The blood uric acid levels in the mothers ranged from 6·9 mg./100 ml. to 2·6 mg./100 ml. and in the infants from 7·3 mg./100 ml. to 2·4 mg./100 ml. In 12 cases the mother's level was higher than that of her infant.

This study shows the rather wide range of blood uric acid levels existing in the cord blood of normal male and female newborn infants and in their healthy mothers' blood taken at the time of delivery; there does not appear to be any correlation between these uric acid levels. In three cases the mother's

TABLE 1

BLOOD URIC ACID LEVELS IN NORMAL MOTHERS AND THEIR FULL-TERM INFANTS AT BIRTH

No.	Maternal Age (yr.)	Parity	Birth Wt. (lb. oz.)	Sex	Blood Uric Acid Level	
					Mother (mg./100 ml.)	Infant (mg./100 ml.)
1	20	Primipara	8.3	M	6·5	5·0
2	20	Primipara	7.9	F	3·6	5·5
3	22	Para 1	7.10	M	4·1	3·9
4	23	Para 1	7.8½	M	4·6	3·4
5	25	Primipara	5.4½	M	2·6	2·4
6	32	Para 1	7.12	M	4·6	4·0
7	33	Para 1	6.15½	M	4·2	5·8
8	18	Primipara	8.8½	M	3·8	3·1
9	23	Primipara	6.4	M	4·9	2·8
10	32	Para 3	7.8½	F	3·9	3·5
11	21	Para 1	7.0½	F	4·7	4·2
12	34	Para 4	7.11½	F	6·7	4·3
13	22	Primipara	7.8	F	3·0	3·8
14	41	Para 10	6.10½	F	6·9	6·5
15	29	Para 1	6.12½	F	3·6	3·8
16	27	Para 1	8.2	F	4·4	4·5
17	22	Para 2	6.10½	F	5·1	7·3
18	37	Para 7	6.6	F	2·6	5·3
19	21	Para 1	5.8½	F	3·9	3·7
20	21	Primipara	7.15¾	F	4·0	4·5
21	29	Para 1	8.2½	F	4·0	5·0

level was over 6 mg./100 ml. and in two infants cord blood levels were also above this figure; only in one case was the level above 6 mg./100 ml. in both the mother and her female infant.

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REFERENCES

Benedict, S. R. (1922). The determination of uric acid in blood. *J. biol. Chem.*, **51**, 187.
Crawford, M. D. (1939). The effect of labour on plasma uric acid and urea. *J. Obstet. Gynaec. Brit. Emp.*, **46**, 540.
Folin, O. and Trimble, H. (1924). A system of blood analysis; improvements in quality and method of preparing the uric acid reagent. *J. biol. Chem.*, **60**, 473.
Praetorius, E. and Poulsen, H. (1953). Enzymatic determination of uric acid. *Scand. J. clin. Lab. Invest.*, **5**, 273.
Steenstrup, O. R. (1956). Hypo-uricemia during pregnancy. *Ibid.*, **8**, 263.

BOOK REVIEWS

Paediatric Neurosurgery. Ed. IRA C. JACKSON and RAYMOND K. THOMPSON. (Pp. xvi + 564. £6 5s.) Oxford: Blackwell Scientific Publications.

There are two ways of writing a textbook on a small specialized branch of medicine. The first is to describe the practice of one particular school, its great virtue being that it sets a standard against which others can measure their own work. Ingraham and Matson have already successfully exploited this technique in their *Neurosurgery of Infancy and Childhood*. The second method is to assemble a team of contributors each of whom speaks of his own subject. Ideally this should lead to increased erudition and brilliance; in practice it tends to sacrifice unity of presentation.

The first few chapters of this book are devoted to a detailed account of various clinical methods. The section on lumbar and ventricular puncture is very full but, rather irritatingly, subdural puncture is dealt with partly here and partly in a later section. There is an interesting account of the use of electromyography; the section on the E.E.G. is so short and so general that it would have been best omitted. The section on anaesthesia lists many possible methods, but gives little practical advice. An interesting innovation is the introduction of a chapter on medical conditions resembling surgical problems, but it is strange to find no mention of Devic's disease here, although the papilloedema seen in this condition may lead to the suspicion of intracranial tumour.

Congenital malformations are dealt with at some length. The advice on the management of spina bifida cystica is clear and sensible but the indications for operation on spina bifida occulta are muddled and the writer has apparently abandoned any effort to classify his results. In the section dealing with encephalocoele, there is the barest mention of hydrocephalus, and none of ultimate mental retardation, though both complications are not infrequent.

In the section on inflammatory diseases the term débridement (of wounds) is used as a synonym for excision, which it is not, and the advice that persistent post-infective subdural effusions should be drained into the pleural cavity is controversial, to say the least. It is also a pity that although the writers of other sections devote much space to the technique of well-known surgical procedures, antero-lateral decompression for the relief of paraplegia in spinal tuberculosis is barely mentioned.

The author of the section on vascular malformations of the nervous system sets out a series of case histories separated by relatively brief general remarks. The result is that although given much useful information,

a reader not already familiar with the subject is left in doubt which of the clinical observations are of general importance, and which apply only to the case described.

The section on intracranial tumours is long and not wholly satisfactory. Most of the references are old (before 1950) and it is unhelpful to refer simply to 'Bailey' when the bibliography lists two different Baileys with eight references between them. I cannot understand the statement that 'medulloblastomas occur almost exclusively in males and the same is true of craniopharyngiomas' (p. 225). In any event it is inconsistent with the further statements that there is no specific sex predilection in craniopharyngiomas (p. 268) and that medulloblastomas are three times more frequent in males than in females (p. 314). The author's views on the prognosis in medulloblastomas are unduly gloomy and take no account of the work of Ralston Paterson and his colleagues.

The section on peripheral nerve tumours, in which is included neuroblastoma, is sketchy and would have been better omitted.

The sections on trauma to the head and spine are both practical, though it is wrong to use 'hypothermia' as a synonym for control of pyrexia and curious that although 3rd and 6th cranial nerve palsies are mentioned, nothing is said about damage to the 4th cranial nerve, which is as common as any post-traumatic oculomotor disturbance. From time to time the contributors, and even the editors themselves, seem to lose sight of the fact that they are writing about infants and children. There is an editorial note in the section on spinal injuries which refers to intervertebral disc herniations as due to a degenerative process: this is surely not the case in children.

There are separate chapters on the surgery of involuntary movements and leucotomy (lobotomy). The wisdom of this is doubtful. The application of the former to paediatrics is not properly worked out, and many would think that the latter should never be practised at all in children. There is also a chapter on the surgery of epilepsy but it is devoted entirely to advice on local resection of the cortex, and the author starts from the proposition that no surgery should be done for epilepsy below the age of 12. The surgery of infantile hemiplegia, particularly hemispherectomy, is nowhere mentioned.

There is much useful material in this book, but it seems to fall between two stools. The paediatrician will find more surgical detail than he needs, while the trained neurosurgeon will find some chapters insufficiently authoritative. In a second edition there should be ruthless pruning, and the standard of the bibliographies at the end of each chapter should be raised.

Lehrbuch der Chirurgie und Orthopaedie des Kindesalters. Ed. A. OBERNIEDERMAYR. (3 vols. Pp. 375, 1087, 266; illustrated DM. 620.) Berlin: Springer Verlag. 1959.

This is by far the largest textbook on paediatric surgery written since the war. It consists of three volumes and more than 1,500 pages, but in spite of its size the book is not as complete as one would expect and some of the chapters are surprisingly small. The largest part of the work of a paediatric surgeon is undoubtedly abdominal surgery and it is, therefore, surprising that only 150 pages are devoted to this subject. The quality of the different chapters varies considerably. Those written by the editor and his paediatric surgical colleagues include accounts of most of the recent advances in this field and describe the personal experience of the writers. The same cannot be said of some of the other chapters written by 'General' and 'Specialist' surgeons. The section on plastic surgery by H. Gelbke is excellent and deserves special praise, but it is obvious that some of the authors have not had much experience with children and are inadequately informed of recent advances in paediatric surgery.

Professor Oberniedermayr has performed a gigantic task in editing this monumental textbook, which will be of value to surgeons and paediatricians alike. It is unfortunate that the high price of the book will prevent most people acquiring it.

Growth Diagnosis. By LEONA M. BAYER and NANCY BAYLEY. (Pp. 241. 80s.) Chicago: University Press. 1960.

The importance of assessing a child's growth progress and developmental status is now widely recognized amongst paediatricians not only in relation to endocrinopathies, chromosomal aberrations and mental retardation, but also in obese children, and children with education problems, operated cardiac conditions, poliomyelitis, spasticity and many other complaints. There exists no succinct guide, however, telling the busy clinician in relatively few words and charts just how to do this. The present book is a praiseworthy, though by no means entirely successful, effort to provide one. It is exceedingly well produced and less excessive in price than most books coming from the United States at present.

The first 68 pages are devoted to descriptions of methods for studying growth in the individual patient, and the next 144 to describing in detail the application of these methods to 22 children, of whom eight are healthy children, followed from birth to maturity in the Berkeley Longitudinal Growth Study, and 14 are children with gigantism, various sorts of dwarfism, pseudohermaphroditism, hypothyroidism, precocious puberty, obesity, castration and hypogonadism. The book is clearly not meant to tell the reader anything much about how a child grows, and has no discussion on growth and the influences of genetics, environment, secular trend and so forth; it is presumed, I imagine, that the reader will be acquainted with one of the texts on growth, or with the excellent chapters devoted to it in Nelson or Holt and MacIntosh.

The measurements advocated are height, weight, sitting height (greatly preferable to the use of span in both authors' and reviewer's opinion), biacromial and bi-iliac diameters. The authors fail to mention the clinically indispensable measurement of subcutaneous fat with calipers, and give illustrations of a quite outdated instrument for measuring the two diameters. A technique of taking front, side and rear view body photographs is given, though the rear view pose adopted by the subject in their illustration has little to recommend it, and the opinion that 'box cameras are preferable' has a quaint Victorian ring. The Greulich-Pyle and Pyle-Hoerr atlases for bone maturity at wrist and knee are recommended and briefly introduced. An anthropometric chart is used in which the five measurements given above are plotted in terms of standard deviations away from the mean. This is incorrect for weight, since the skew in its distribution makes the standard deviations *not* correspond to the usual percentiles; in any case, percentile charts are easier to understand for all measurements. The tables used as the basis for mean values and standard deviations date from 1931 (the Gray-Ayres data) which, considering the great secular trend over the last fifty years, is surprising. Scales for rating secondary sex character appearance are given, but in boys no distinction is made between ratings for pubic hair and genitalia, though the two do not always exactly keep step with each other. There is a long section describing the authors' own excellent work on androgyny of build, and another giving Dr. Bayley's very useful tables for prediction of adult height from height and skeletal development during childhood. There are also, and interestingly, new standard charts of height and weight for age, from birth to maturity, in which a most praiseworthy effort is made at including information on the developmental as well as the chronological age of the child. Lines are given for the physically accelerated and retarded child as well as for the average; the difficulty would seem to be that one cannot distinguish on them a pathologically small child from a pathologically retarded one, as one can by plotting height on a conventional chart in terms first of chronological, then of skeletal, age.

The clinical material is of great interest, illustrated with excellent photographs, and followed for the most part over long periods of time. Despite the criticisms above, there is no question that these descriptions constitute the best published accounts to date, from the growth point of view, of cases with clinical growth disorders. This is indeed what anyone familiar with the authors' work and particularly with Dr. Bayley's many and deeply thought out papers on physical and mental growth would expect. It is the more pity that a rather critical review is unavoidable. A curious insularity seems to have settled over the Bay when the book was written; astonishingly, only four references appear to papers published outside America; one of these refers to Fröhlich's original paper of 1901; the other three to standard texts of over twenty-five years ago, all of which have been reissued since in later editions. The authors are certainly to be congratulated on essaying a very necessary task; the result, despite blemishes, which will doubtless be removed in the second edition, is well worth the attention of paediatricians.

Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants—Full Term and Premature. By B. LEVIN, HELEN M. M. MACKAY, CATHERINE A. NEILL, V. G. OBERHOLZER and T. P. WHITEHEAD. (16s.) Medical Research Council, Special Report Series No. 296. 1959.

This is a valuable report which should help to set standards and remove a lot of uncertainty. The clinical material was composed of over seven hundred babies, over two-thirds full term and under one-third premature, almost all born at the Mothers' Hospital in North-East London. The mean weights of the full-term infants are similar to those of published standards for 'normal' infants, but the smoothed curves now presented are a valuable addition to the somewhat scanty British data on this subject. The curves for premature babies confirm the view that if weights are grouped by age from conception, then after 40 weeks the curve is similar to that for full-term infants. As regards feeding it is generally concluded that full-term babies in this series, fed either on breast milk or on dried cows' milk, had similar weights, similar protein levels, a similar incidence of infections and, with iron medication, similar haemoglobin levels. For premature babies, however, it is concluded that human milk is an inadequate food in early life, due to the low protein content. Biochemical investigations established standards of normal for total serum protein, albumin and globulin in the first eighteen months of life in full-term infants. The serum protein levels of premature infants were much lower than for full-term infants but changes for age were similar in both. After eight days of age the serum protein level was not influenced by the type of food given. Valuable data on the serum protein components and especially on serum gamma globulin levels in the cord blood are also included. The whole report represents a great amount of co-ordinated labour and must be regarded as a standard work of reference.

A Symposium on Immunization in Childhood. (Pp. 139. 17s. 6d.) Edinburgh: Livingstone. 1960.

After protracted discussion the symposium adopted two schedules for immunizing children. The first was, 5 weeks to 6 months—three injections of pertussis vaccine; 7-10 months—two injections of poliovaccine; 10-12 months—two of diphtheria and tetanus and a fourth of pertussis; 15-18 months—a third injection of diphtheria and tetanus and of poliovaccine. Booster doses of diphtheria and tetanus at school entry and 8-9 years. The second schedule was, 2-6 months—three injections of a triple vaccine of diphtheria, tetanus and pertussis; 7-10 months—two injections of polio; 15-18 months—a fourth injection of the triple vaccine and a third of polio; booster doses of diphtheria and tetanus as for schedule 1. In each schedule smallpox vaccination was to be carried out some time during the first 5 years, with re-vaccination at 8-9 years, and B.C.G. was to be given between 10 and 15 years. Schedule 1 entails 11 visits and 13 injections, while schedule 2 needs nine visits and 10 injections.

Both these are formidable programmes, demanding much of the public health authorities and not a little of the mothers and children, not to mention the fathers. The fact that two schedules had to be promulgated shows how opinion can be divided, and the pros and cons of each in relation to the different disease vaccines are fully and freely discussed in the text. All through there is evidence of the desire to confer optimum protection with the minimum of backsliding on the part of the patient, and this is clearly why the two different schedules are propounded.

This publication is most timely and will help to some extent to delimit the problems concerned with vaccination programmes even if the tentative answers to them are somewhat equivocal. And as with so much recent writing, one is left with the feeling of what an unpleasant person in the woodpile is type 1 polio virus.

1959-60 Year Book of Pediatrics. Ed. SYDNEY S. GELLIS. (Pp. 493. 60s.) Published by Year Book Publishers, Chicago, and distributed by Interscience Publishers, London.

Dipping into this year book is just like going to an international paediatric congress in the United States. It does not matter which particular section one attends, there is the same series of well-chosen papers, generally of the proper length but some overrunning their time, some passing without comment but others attracting discussion. Naturally the majority of the papers are by Americans, and all the commentators are American also.

The congress has various things, such as personal contacts and 'cokes', which the book lacks; but these apart, I believe one could profit as much by reading the book as by attending the congress—and it is a lot cheaper.

Actualités Pédiatriques, 1ère série. Ed. MARCEL LELONG. (Pp. 323; 63 figs. Fr. fr. 3,900.) Paris: G. Doin et Cie. 1959.

From the Hospital of Saint-Vincent de Paul comes a series of 19 chapters by different authors dealing with one or other of the growing points of paediatrics. Each article is complete in itself and, while not exhaustively reviewing its subject, is a reasonably full account of recent work. The volume is sponsored by Professor Marcel Lelong who himself contributes a chapter on hiatus hernia. These articles give one a rapid appraisal of a particular subject but would not be a jumping-off ground for further research as they do not assess the literature to any degree.

Sewage Contamination of Bathing Beaches in England and Wales. (Pp. 24. 2s. 6d.) Medical Research Council Memorandum No. 37. London: H.M.S.O. 1959.

Readers of this pamphlet will be relieved to learn that the danger of contracting infectious illness from bathing where sewage is discharged into the sea is negligible.

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